ONE-ELECTRON REACTIONS INVOLVING ORGANOTIN AND SILICON HYDRIDES

By

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Dedicated to

Tony Bennett, Frank Sinatra, Al Martino, Nat King Cole
and Dean Martin for their moving music

The Temptations, Four Tops and Marvin Gaye
for their soul and inspiration

My family for their support
and belief in me

ACKNOWLEDGMENTS

Frequently, I look back to my first chemistry course at Central High School in Grand Rapids, Michigan. It is never without a chuckle that I remember Mr. Lubbers, the chemistry teacher who first taught me about atoms, molecules and the wonders of chemistry. He used to tease us by imitating a student, and would claim in a whiny voice, “Mean ‘ol Lubbers! You give us all this darned homework!” His good humor and broad smile made it a pleasure to learn about the basics of chemistry.

My undergraduate career at Michigan State University was a very nurturing period in my life. Dr. Paul Hunter, Dr. Chi Chang, and especially Dr. Eugene LeGoff were instrumental in allowing me the freedom of independent laboratory research. These gentlemen were very supportive and provided access to many different areas of chemistry, to which I might not have been privy otherwise. I also enjoyed working with graduate students Mike Waldo and Craig Shiner, who knew how to appreciate a good cigar.

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Requirements for the Degree of Doctor of Philosophy

ONE-ELECTRON REACTIONS INVOLVING ORGANOTIN AND SILICON HYDRIDES

By

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December 1998

Chairman: Dr. Eric Enholm
Major Department: Chemistry

Many novel developments have been made for single-electron reactions of trialkyltin and trichlorosilicon hydrides. A study was conducted involving several hydride reagents and their effectiveness at diastereoselectively reducing ketones. Development of a polymer-support tin chloride reagent was completed, enabling catalytic reduction of organohalides with sodium borohydride ($NaBH_4$). Cyclization of acetylene-tethered enones was accomplished via a carbomercuration reaction, using tributyltin hydride (Bu_3SnH). Employing Bu_3SnH to open [2+2] photoadducts allowed access to medium ring bicyclic and linear tricyclic systems. Finally, triethylborane (Et_3B) initiated, low-temperature radical conditions were investigated for use with Bu_3SnH.

A new highly diastereoselective reduction of α-hydroxy ketones to anti-1,2-diols had been examined under free radical conditions. Using the Inexpensive and convenient reagent trichlorosilane, the oxygen directed reduction gave anti : syn diastereomer ratios of 63 : 1. This ratio exceeded that of both one-electron reagents such as Bu_3SnH and tris(trimethylsilyl)silane (TTMSS), and also common hydride reagents such as sodium borohydride ($NaBH_4$) and lithium aluminum hydride ($LiAlH_4$). A mechanistic discussion of the α-hydroxyketone reduction was also proposed.

A convenient non-crosslinked polymer-support tin chloride reagent was developed which showed excellent catalytic properties for reducing a variety of alkyl halides with $NaBH_4$. It was found that the tin polymer could be used at 1% mol. equiv, and still was an efficient catalyst providing high yields (74-99%) of the alkane products. The synthesis of the tin reagent was also high yielding and facile. The catalytic nature of this new reagent will be discussed, including a mechanistic proposal.

The objective of another project was to develop a methodology, that may produce several unique β,γ-unsaturated cyclic ketones. Our new methodology proceeded with Bu_3SnH, from easily synthesized α,β-unsaturated ketone precursors. The use of Hg (II) allowed for lower reaction temperatures.

Furthermore, a study into low-temperature tributyltin radical reactions was made. The use of Et_3B and air to initiate the radical process was successful and allowed reactions to proceed at temperatures ranging from –78°C to 25°C.

Examples of reductive intermolecular alkylation of aldehydes will be discussed.

Mechanistic aspects of these reactions will also be covered.

CHAPTER 1
INTRODUCTION

Free Radical Chemistry

In the past, traditional chemists employed ionic reactions to affect their organic transformations. Although cationic and anionic species are well understood, their inability to react with *"like charges"* and the problems associated with solvation effects became apparent. In the last couple of decades, radical reactions have generated interest and became an important asset to the experienced chemist. Often radical-mediated reactions are run under neutral conditions, and can be a great advantage to a chemists' repertoire. Unlike anionic processes, which may epimerize stereo centers, radical processes forego this particular hazard.

Although they are neutral species, free radicals exhibit a wide variety of chemical reactivity. The nature of the radical's character is due, in part, to the atom in which the unpaired electron resides. Silicon and tin radicals are the basis of this study, and their inherent reactive properties will be the focus of this publication. Several summaries are now available which highlight the current trends and theories in radical chemistry.[1]

As can be seen from **Table1-1**, the bond dissociation energies (BDE), for the homolytic cleavage of the hydrogen bonds in several hydrides, may be compared.[2] The values give insight into the effects which the substituents have on homolytic cleavage of the hydrogen atom. Tributyltin hydride, with BDE = 74, is one of the most frequently used radical species in organic chemistry. Due to its low BDE, tributyltin radical can be formed easily and is relatively stable. Tris-trimethylsilyl silane (TTMSS), with BDE=79, is a competitive silicon analogue to tributyltin hydride and shows very similar reactive qualitites.[2,3] Triphenyl silane, triethyl silane, and trichlorosilane all have higher bond dissociation energies (84-91 kcal/mol), and are known to produce less stable silicon radicals, but there is ample evidence of their use as viable reagents for radical processes.[2c,4]

Table 1-1. Physical Properties of Hydride Reagents

Hydride	BDE (kcal/mol)
$Bu_3Sn\text{-}H$	74
$(Me_3Si)_3Si\text{-}H$	79
$Ph_3Si\text{-}H$	84
$Et_3Si\text{-}H$	91
$Cl_3Si\text{-}H$	91

The initiation of homolytic cleavage of the hydrogen bond may be approached by two distinct courses (**Scheme 1-1**). Chemical initiation is the most common, since the reagents are readily available and no special apparatus is necessary. Common chemical initiators include di-t-butyl peroxide, di-t-butyl peroxalate, t-butyl perbenzoate, dibenzoyl peroxide, and azobisisobutyronitrile

(AIBN) **1-1**. For example, in the chemical initiation process, AIBN **1-1** is thermally activated (losing N_2 (g)) to produce 2 equiv of isopropyl cyanide radical **1-2**. H-atom abstraction by **1-2** from tributyltin hydride **1-3** (or another silicon hydride) yields isopropyl cyanide **1-4** and the desired tributyltin radical **1-5**.

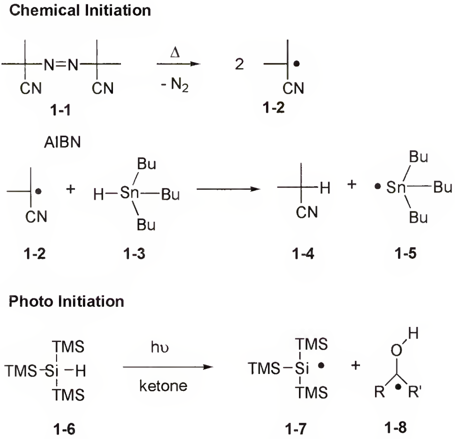
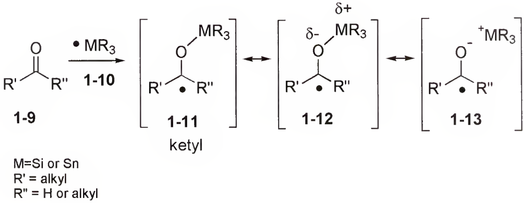

Chemical Initiation

Photo Initiation

Scheme 1-1. Formation of Tin and Silicon Radicals

In certain cases, low-temperature conditions are required which would make thermal initiation impractical. Alternatively, photochemical initiation may be exercised to begin the desired sequence. UV light is used to promote the ketone substrate to an excited singlet state. After a series of steps, the ketone diradical reacts with the hydride reagent tris(trimethylsilyl)silane (TTMSS) **1-6** (or a similar hydride), which is converted to the expected tris(trimethylsilyl)silane radical **1-7** by rupturing the silicon-hydrogen bond. Oftentimes, chemical initiators like AIBN and dibenzoyl peroxide are found to be particularly useful in conjunction with photochemical methods to initiate a radical sequence.[1a]

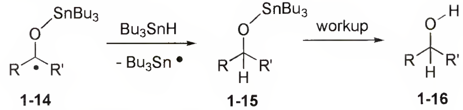
Trisubstituted silicon and tin radicals **1-10** react in numerous ways, adding reductively to aldehydes and ketones **1-9** (**Scheme 1-2**), for example. Initially, a species known as a 'ketyl' **1-11** is formed, which bears a carbon-centered radical. The ketyl intermediate has several resonance structures which may depict its true transient nature. Since there is a difference in electro-



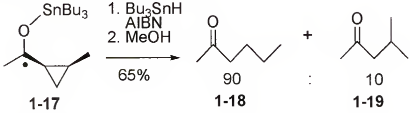
Scheme 1-2. Formation of Ketyls

negativity between the oxygen and silicon or tin, the O-M bond is expected to display some ionic character (structures **1-12** and **1-13**). This electronic contribution to the ketyl radical will influence its mode of reactivity.

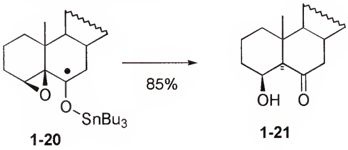
Simple Reduction



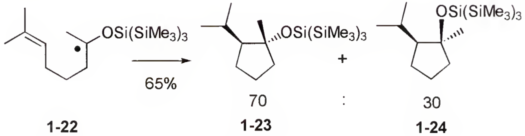
Cyclopropane Ring Opening



Epoxide Ring Opening



Cyclization



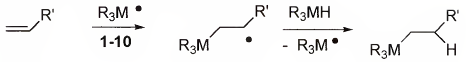
Scheme 1-3. Reaction of Ketyls

Once formed, ketyls can undergo several different organic transformations. As seen in **Scheme 1-3**, simple reduction of the ketyl species **1-14** is made possible by abstraction of an H-atom from the hydride reagent. The resultant tin ether **1-15** then provides an alcohol **1-16** upon workup.[5] Cyclopropane rings adjacent to the ketyl **1-17** can be opened, to eventually yield an acyclic ketone **1-18** or **1-19**.[6] Pete proved that in a similar fashion, an epoxide ring **1-20** can opened to give a β-hydroxy ketone **1-21** in good yield.[7] Ketyls are also commonly used for cyclization onto a tethered olefin **1-22** to access cyclic products **1-23** and **1-24**, as shown by Kulicke and Giese.[8]

The regiochemical reactivity of silicon and tin radicals **1-10** with olefins is strongly dependent upon the substituents of the double bond. Alkyl substituted olefins **1-25**, **Scheme 1-4**, are attacked at the least hindered carbon by **1-10**, to give the more stable radical intermediate **1-26**. Chain transfer by H-atom abstraction then allows for net anti-Markownikoff addition product **1-27**. Olefins next to carbonyl groups react differently, according to the nature of the carbonyl. Conjugate addition with α,β-unsaturated esters, amides and carboxylic acids **1-28** is known in the literature, giving predominantly the β-substituted product **1-30** via radical **1-29**.[9a] Conversely, silicon and tin radicals **1-10** undergo 1,2-addition with α,β-unsaturated aldehydes and ketones **1-31**.[9b-d] First, an allylic O-stannyl ketyl (or O-silyl ketyl) **1-32** is formed, which is in resonance with the tin enolate radical **1-33** (or silyl enolether radical). The intermediate **1-33** abstracts H-atom from the hydride reagent next to give the enolate **1-34**.

Advantage can be taken of the enolate **1-34**, made during the radical process. The Enholm research group has exploited the reactivity of this

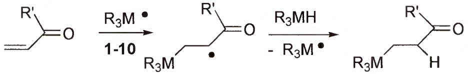
Addition to Alkyl-Substituted Olefins



1-25 **1-26** **1-27**

M= Si or Sn; R = alkyl, halogen; R' = H or alkyl

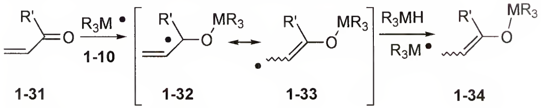
Conjugate Addition with α,β-Unsaturated Esters, Amides and Carboxylic Acids



1-28 **1-29** **1-30**

M= Si or Sn; R = alkyl, halogen; R' = OR, NR_2, or OH

1,2-Addition with α,β-Unsaturated Aldehydes and Ketones

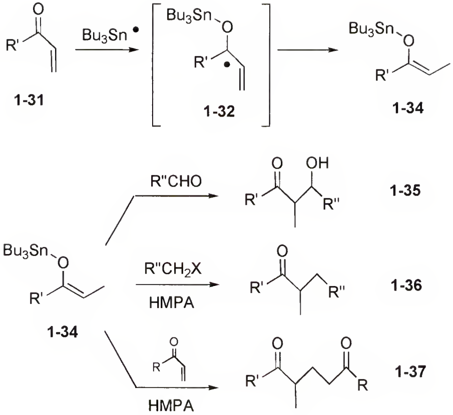


1-31 **1-32** **1-33** **1-34**

M= Si or Sn; R = alkyl, halogen; R' = H or alkyl

Scheme 1-4. Tin and Silicon Radical Reactions with Olefins

nucleophilic intermediate by reaction with several electron-accepting substrates (**Scheme 1-5**).[9b-d] Tributyltin enolate **1-34**, generated *in-situ*, has been reacted with aldehydes to form aldol products **1-35**. Reaction of **1-34** with primary alkyl halides is a convenient technique to monoalkylate **1-36** ketone substrates regioselectively. Finally, 1,4-addition of tin enolate **1-34** onto unsaturated carbonyls has been demonstrated to give Michael products **1-37**.



Scheme 1-5. Reaction of Tin Enolates

Silyl and stannyl radicals are also known to react with other, non-carbonyl functional groups (**Scheme 1-6**). Their use in efficiently reducing alkyl halides **1-38** (R = halogen) is widespread. The trisubstituted stannyl or silyl radical **1-10** may react with thioethers, selenides, and nitroalkanes **1-38** too. This procedure involves generation of the tin or silicon radical **1-10**, which then abstracts the heteroatom from **1-38**, giving tetrasubstituted **1-39** and alkyl radical **1-40**. The highly reactive alkyl radical **1-40** can then experience H-atom abstraction from the hydride **1-41**, yielding the reduced alkane **1-42** and regenerating silyl or stannyl radical **1-10**.

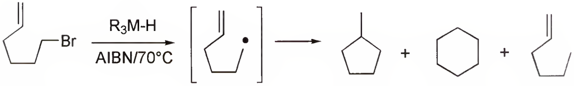
$$\underset{\textbf{1-10}}{R_3M\bullet} \quad + \quad \underset{\textbf{1-38}}{R'\text{-}X} \longrightarrow \underset{\textbf{1-39}}{R_3M\text{-}X} \quad + \quad \underset{\textbf{1-40}}{R'\bullet}$$

$$\underset{\textbf{1-40}}{R'\bullet} + \underset{\textbf{1-41}}{R_3M\text{-}H} \longrightarrow \underset{\textbf{1-42}}{R'\text{-}H} + \underset{\textbf{1-10}}{R_3M\bullet}$$

M = Si or Sn
X = halogen, -SR", -SeR", -NO_2

Scheme 1-6. Reductions with Silyl and Stannyl Radicals

This useful process has been applied to ring formation by radical closure onto an olefin. As seen in **Scheme 1-7**, an olefinic alkyl halide **1-43** can react under standard radical conditions with a silicon or tin hydride to form an intermediate alkyl radical **1-44**.[2] The radical **1-44** can then attack the olefin



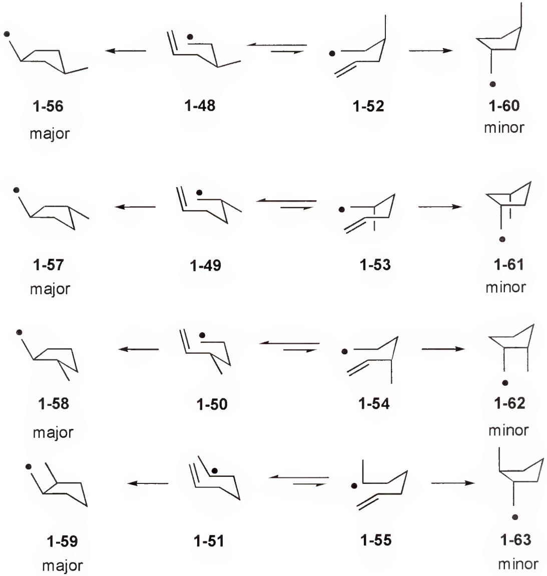
1-43 **1-44** **1-45** **1-46** **1-47**

	1-45	1-46	1-47
$(Me_3Si)_3SiH$	93%	2%	4.1%
Bu_3SnH	83%	1.2%	15%

Scheme 1-7. Radical Ring Closures

appendage to predictably give the kinetically favored cyclopentane product **1-45** predominantly over of the cyclohexane product **1-46**. Minimal amounts of the uncyclized **1-47** were reported as well. In his studies, Chatgilialoglu obtained similar results using TTMSS (**1-6**) and tributyltin hydride (**1-3**).

5-Exo-trig cyclizations, which are allowed by Baldwin's rules for ring closure, are known to be faster than 6-endo-trig cyclizations.[10] The behavior of



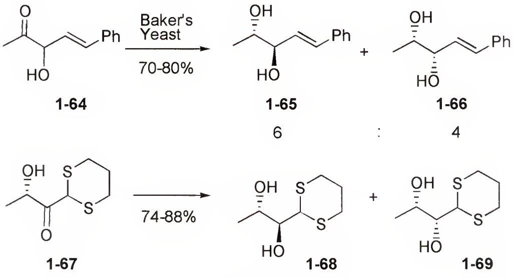
Scheme 1-8. Beckwith Chair Model for 5-exo-trig Cyclizations

radical ring closures can be predictably ascertained by use of the Beckwith chair model.[1a] **Scheme 1-8** portrays the concept of the pseudo-chair transition state, where the methyl substituent prefers an equatorial position **1-48** to **1-51**.

Cyclization of these intermediates then gives access to cyclopentanes **1-56** through **1-59**, respectively, as the major products. An equilibrium exists between the equatorial-substituent transition states, **1-48** to **1-51**, and the axial-substituent transition states, **1-52** to **1-55**. This equilibrium falls far to the left. Cyclization of the axial-substituted conformers gives rise to the minor cyclopentane products **1-60** to **1-63**.

Traditional Synthetic Methods

Directed reduction of carbonyl compounds is known in the literature. Neighboring-group participation has been shown to allow for chelation control, where a particular stereoisomeric product is favored by external delivery.[11] As



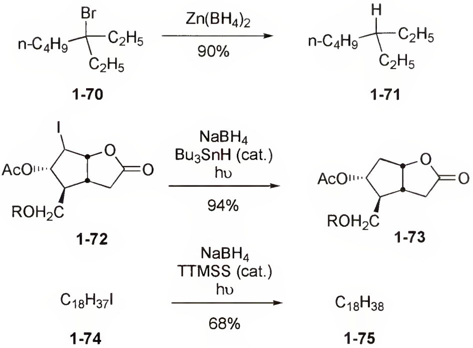
	1-68	1-69
NaBH4	36	64
LAH	69	31
DIBAL	89	11

Scheme 1-9. Directed Reductions of Ketones

seen in **Scheme 1-9**, reduction of α-hydroxy ketones has been done both enzymatically and with traditional two-electron reducing agents. In work done by Fuganti and coworkers, baker's yeast reduced α-hydroxy ketone **1-64** to **1-65** and **1-66**, in a ratio of 6:4.[12a] A study was made by Fujisawa to reduce **1-67** to diol diastereomers **1-68** and **1-69**, with common hydride reagents.[12b] Moderate to good diastereoselective ratios favoring anti-diol **1-68** were obtained. Although these ionic hydride reducing agents are often effective, their basic nature can cause problems with certain types of substrates.

As explained above (**Scheme 1-3**, **1-16**) tributyltin is capable of reducing aldehydes and ketones selectively, under mild, neutral reaction conditions. In an effort to find a less toxic alternative to tributyltin hydride, Chapter 2 examines the use of a variety of silicon hydrides as reducing agents for aldehydes and carbonyls. Comparison of these radical reducing agents will show that trichlorosilane is superior in its performance, giving the best overall results for diastereoselectively reducing α-hydroxy ketones to vicinal diols. Studies, which support an external hydrogen atom delivery mechanism, will be discussed.

Reductions of alkyl halides to their corresponding alkane products is an important chemical reaction.[13a] Zinc borohydride ($Zn(BH_4)_2$) has been shown to be effective at dehalogenation of several alkyl halides (**Scheme 1-10**).[13b] Corey was one of the first researchers to use a catalytic amount of tributyltin hydride with $NaBH_4$, to effect the reduction of **1-72** to **1-73**.[13c] In a similar application by Chatgilialoglu, $NaBH_4$ was used with a catalytic amount of TTMSS to convert alkyl iodide **1-74** to **1-75** under photolytic conditions.[3b]



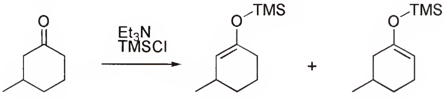
Scheme 1-10. Reductions of Alkyl Halides

In order to reduce the heavy metal toxicity of tin which is commonly employed in most free radical processes, Chapter 3 focuses on creating a non-crosslinked, polymer-supported tin reagent. Conditions for catalytic use of the tin polymer were developed, and their effectiveness for reducing alkyl halides will be explored. The ease of limiting tin byproduct contamination by selectively crystallizing out the polymer will also be discussed.

Enolates are significant reactive intermediates, which are often used as building blocks for C-C bond formation. Typically, ketone enolates are formed under very basic conditions and can lack regiochemical control, when both sides of the carbonyl offer acidic hydrogens. As seen in **Scheme 1-11**, ketone **1-76** may form two distinct enolates, which can be trapped with trimethylsilyl chloride

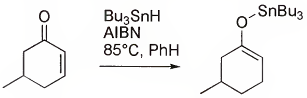
(TMSCl) to give two silylenol ethers **1-77** and **1-78**. In contrast, enones of type **1-79** may react under standard tin radical conditions to form a single tin enolate **1-80**. This reactive intermediate is generated *in situ*, and has a predictable regiochemistry.

Basic Conditions



1-76 **1-77** **1-78**

Neutral Free-Radical Conditions



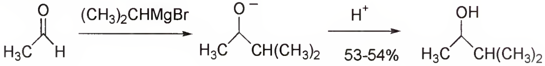
1-79 **1-80**

Scheme 1-11. Enolate Formation

Chapter 4 details the synthesis of an assortment of enone substrates. The reaction of these enones with tributyltin hydride, to form tin enolates will be analyzed. The subsequent cyclization of the enolates with tethered acetylenes, by use of carbomercuration chemistry, are shown to be effective for certain starting materials. The avoidance of competing products will also be presented.

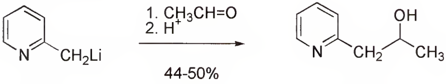
Chapter 5 attempts to access medium ring bicyclic and linear tricyclic products from ketyl intermediates. A group of [2+2] photoadducts were synthesized as precursors for the radical reactions. The expected cyclobutane ring opening should provide a tin enolate intermediate with a distant carbon-centered radical. The results for the cyclobutane ring expansion process and mechanistic considerations will be indicated.

Grignard



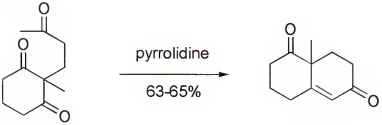
1-81 **1-82** **1-83**

Alkyl Lithium



1-84 **1-85**

Enolate



1-86 **1-87**

Scheme 1-12. Carbon Nucleophilic Attack on Aldehydes and Ketones

Nucleophilic attack on aldehyde and ketone substrates is a common method to create C-C σ-bonds (**Scheme 1-12**).[14] Several processes are available, encompassing a wide variety of carbanion reagents, including; Grignards, alkyl lithiums, enolates (i.e.: Robinson annulation), etc. Although these techniques have become extremely useful to the synthetic chemist, they often entail very basic conditions which may be detrimental to certain substrates.

Chapter 6 investigates the prospect of using triethylborane as a chemical initiator for low-temperature radical reactions. A new technique for C-C bond formation with aldehyde carbonyls was developed under non-basic conditions. For the first time, an example of an alkyl radical's addition to an activated aldehyde, under Et_3B conditions, will be presented.

CHAPTER 2
DIASTEREOLECECTIVE REDUCTION OF KETONES USING TRICHLOROSILANE

Background

Today chemists are encouraged to become more responsible with their developments. Environmental issues are on the forefront of concerns; with 'green chemistry' and 'enviro-economics' being topics of importance.[15] Industry is driving towards cleaner and safer chemistry, due to political and societal standards that have changed our outlook on the effects of toxins being produced. For this reason, silicon chemistry appears to be an appealing alternative to its tin analogues, due to the relative benign qualities of their reagents and the byproducts being produced.[*, 16]

Silicon hydride chemistry has been established for several decades.[17] Many different transformations have been accomplished employing radical-based silicon hydride chemistry. As seen in **Scheme 2-1**, these include hydrosilation of olefins,[18] halogen atom abstraction,[2] and addition to simple ketones.[3c] As the use of silicon hydrides increases and our understanding of their properties develops, newer and better silane reagents can be designed.

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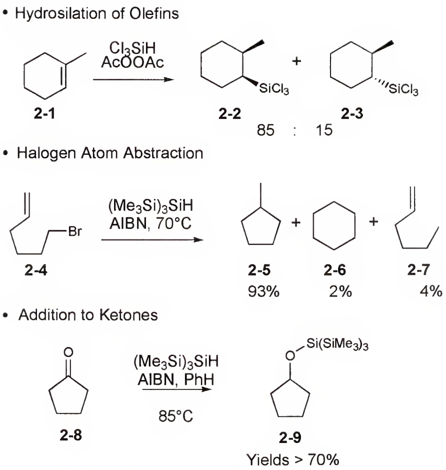
[*] The permissible ACGIH Threshold Limit Value (1980) in air for tributyltin hydride: TWA federal standard is 0.1 mg(Sn)/m^3(skin); the tentative STEL is 0.2 mg/m^3; the IDLH level is 200 mg/m^3. In comparison, the permissible exposure limits in air for silanes: no federal standards exist; recommended TWA for silane of 5 ppm (7 mg/m^3), but no STEL value is given (for elemental Si, ACGIH recommends a tentative STEL of 20 mg/m^3).[16 b,c]



Scheme 2-1. Silicon Hydride Reactions

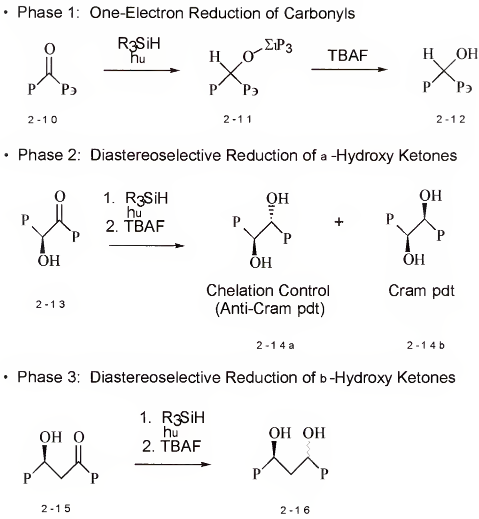
Since the development of tris(trimethylsilyl)silane (TTMSS) by Gilman,[19] a new era of silicon hydride chemistry has been established. Although costly, TTMSS has become an important replacement for tri-n-butyl hydride for radical reductions of organic compounds, due to convenient purification of products, as compared to the tin analogues.[20] Chatgilialoglu has done extensive kinetic studies of this relatively reactive silane in the 80s and 90s.[2, 3b, 3c, 17a]

This paper will show that a simple and convenient method for reducing α-hydroxyketones was developed using the inexpensive and readily available trichlorosilane reagent. The reduction of ketones is shown to go by a radical process and the oxygen directed reduction of α-hydroxyketones gives rise to a predictable anti-Cram type product. The following methodology provides a higher diastereoselectivity than the well-established two-electron reductions with $LiAlH_4$ or $NaBH_4$, as well as the more expensive one-electron reducing agent tris(trimethylsilyl)silane (TTMSS). This is the first known comparative study between various silicon hydrides and hydride donors such as $NaBH_4$ for a directed reduction of ketones to alcohols.

The use of TTMSS in a modern chemist's arsenal is limited because of its high cost. It was our endeavor to find an alternative silicon hydride reagent that was cheaper, with better selectivity, similar reactivity, and displaying all the same advantages as TTMSS. Moreover, we wanted to develop a silane that has Lewis acid properties, where directed reductions could be utilized. We believe that trichlorosilane is just such a reagent for the reduction of ketone functionalities, as will be demonstrated in this chapter.

It was noted that little has been done to explore stereoselective hydrosilation of ketones and no work has been done on oxygen-directed reductions with silanes. The work done by Kulicke and Giese[8] in this regard, as well as studies made by Kraus and Liras[4a] with trichlorosilane were the foundation of our present investigation. In particular, comparative analyses of several different silicon hydrides reacting with a single substrate have seldom been reviewed.[3c]

As seen in **Scheme 2-2**, the first phase of our inquiry involved the study of different silicon hydrides and their efficiency at reducing a simple ketone **2-10**. Under the radical conditions used, silylether intermediates of type **2-11** are produced, but often the free alcohol is the desired product. A simple one-pot



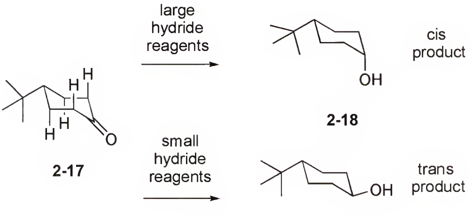
- Phase 1: One-Electron Reduction of Carbonyls
- Phase 2: Diastereoselective Reduction of a -Hydroxy Ketones
- Phase 3: Diastereoselective Reduction of b -Hydroxy Ketones

Scheme 2-2. Silicon Hydride Reduction of Ketones

procedure using TBAF will easily cleave the silicon-oxygen bond to afford the target alcohol **2-12**. In Phase 2 of this research, asymmetric reduction of α-hydroxy substituted ketones **2-13** was attempted with a variety of silicon hydrides. Analysis indicated whether anti-Cram product **2-14a** or Cram type product **2-14b** was preferred and which reagent was most effective. Finally in Phase 3 of this project, an attempt was made to exercise this selective reduction towards β-hydroxy ketones **2-15**.

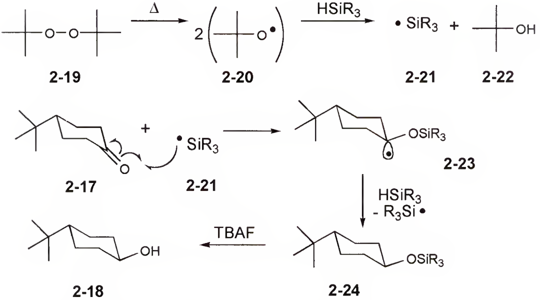
Reduction of 4-t-Butylcyclohexanone with Several Reducing Agents

The effects of standard hydrides on reducing sterically biased ketones have been established for quite some time. For model studies, 4-t-butylcyclohexanone (**2-17**) is often used as a standard substrate (**Scheme 2-3**). Large two-electron reducing agents (like the selectrides) will choose to avoid 3,3-diaxial interactions and mainly give the kinetic cis **2-18** product. In contrast, small two-electron reducing agents, such as $NaBH_4$ and $LiAlH_4$, prefer to give the thermodynamic trans **2-18** product.[21]



Scheme 2-3. Standard Hydride Reduction of Ketones

A simple case study was first done by comparing the reduction of **2-17** with radical reducing agents such as tri-n-butyltin hydride and several silicon hydrides. The commonly used $NaBH_4$ was also examined. The radical chain process for one-electron reduction is shown in **Scheme 2-4**.[8] Upon formation of the silyl radical **2-21** from reaction with the t-butoxy radical **2-20**, addition to the ketone **2-17** occurs forming a Si-O bond. This siloxyalkyl radical **2-23** is expected to adopt the more stable conformation, with the siloxy substituent in the

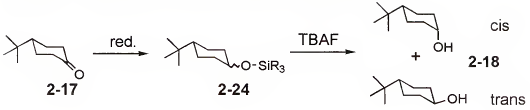


Scheme 2-4. Silyl Radical Reduction of Ketones

equatorial position.[22] Next, hydrogen atom abstraction from another molecule of silicon hydride occurs, yielding the trans product **2-24** as the major isomer. Subsequent cleavage of the Si-O bond with tetrabutylammonium fluoride (TBAF) provides *trans*-4-t-butylcyclohexan-1-ol **2-18**.

Table 2-1 illustrates the preference for all reagents to give the trans product, as expected. Only in the case of TTMSS was the silylether intermediate **2-24** conveniently isolable in high yields. Although sodium borohydride is most commonly used for such reductions, it displayed lower diastereomeric selectivity (85:15, trans/cis resp.) than most of the reagents studied. Trichlorosilane showed the similar facial selectivity for reducing the

Table 2-1. Reduction of 4-t-butylcyclohexanone



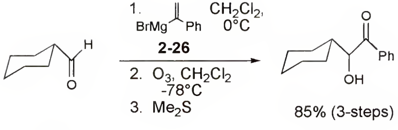
Red. Agent	Initiator	Initiator Equiv.	Time (hr)	Condits	Yield of (2-24)†	Yield of (2-18)*	Pdt. Ratio (trans:cis)
$NaBH_4$	-	-	1.5	rt, EtOH	-	Quant	85:15
TTMSS	AIBN	0.5	10.5	$h\nu$	95%	66%	92:08
Cl_3SiH	-	-	16	$h\nu$	-	82%	82:18
Ph_3SiH	AIBN	0.5	9	110°C, Tol.	-	50%	91:09
Et_3SiH	$(t\text{-}BuO)_2$	1.0	36	$h\nu$	-	13%	100:0
Bu_3SnH	$(t\text{-}BuO)_2$	0.5	16	110°C	-	81%	90:10

† for silylethers 2-24**a**-d (corresponding to entries 2-5); R = $SiMe_3$, Cl, Ph, Et, resp. Only 2-24a (R=$SiMe_3$) was isolated.
* overall yield for 2-step conversion of **(2-17)** to **(2-18)**

simple ketone (82:18, trans/cis resp.), and had the highest yield among the silicon and tin hydrides (82%). The slow reactivity of triethylsilane and its low yield makes it unsuitable for use as a ketone reducing agent, under the conditions studied.

Oxygen-Directed Reduction of Hydroxy Ketones

The next goal was to explore the possibility of substituent-directed reduction of ketones with an α-hydroxy group on the substrate. **Scheme 2-5**



2-25 **2-27**

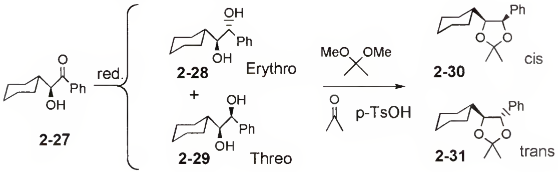
Scheme 2-5. Synthesis of α-hydroxyketone

shows the synthesis of 2-cyclohexyl-2-hydroxy-1-phenylethanone (**2-27**) used in the study. Cyclohexanecarboxaldehyde (**2-25**) was reacted with 1-magnesium bromide ethenyl benzene (**2-26**) at 0°C.[23] Ozonolysis of the resulting allyl alcohol under standard conditions and workup with methyl sulfide provided the desired hydroxy ketone **2-27** in 85% overall yield.

Stereoselective reduction of **2-27** was examined, comparing $NaBH_4$, $LiAlH_4$, TTMSS, Cl_3SiH, and Bu_3SnH (**Table 2-2**). In all cases, yields of the diol products were very good. Separation of erythro diol **2-28** and threo diol **2-29** was not possible by GC on a DB-5 column, so derivation to the acetonide ketals was necessary. This was achieved by reacting the mixture of **2-28/2-29** with 2,2-dimethoxypropane, acetone and a catalytic amount of p-TsOH. As seen in **Table 2-2**, the erythro and threo diols produced cis **2-30** and trans **2-31** ketals respectively. The ratio of **2-30/2-31** could easily be determined by GC analysis.

Among the silane reducing agents, trichlorosilane gave a superior yield of the ketals **2-30/2-31** (93%). Most interestingly, of all reagents studied, trichlorosilane displayed the best diastereoselectivity (63:1, cis/trans resp.) - a higher value than the commonplace two-electron reducing agents, $NaBH_4$ (20:1) and $LiAlH_4$ (17:1). Curiously, TTMSS showed almost no preference (1:1, cis/trans resp.) in the diastereoselective reduction of **2-27**.

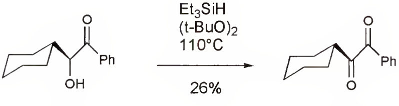
Table 2-2. Diastereoselective Silane Radical Reductions of α-Hydroxyketone (2-27)



Reducing Agent	Equiv.	Time (h)	Conds.	cis : trans (2-30/2-31)	Yield
$(Me_3Si)_3SiH$	1.2	16	110°C	1 : 1	47%^{c}
Cl_3SiH	4.0^{d}	16	$h\nu$	63 : 1	93%^{a,b}
Ph_3SiH	2.0	72	110°C, tol.	-	-^{e}
Et_3SiH	4.0^{d}	16	110°C	-	-^{e}
$NaBH_4$	1.1	1.5	EtOH	20 : 1	
$LiAlH_4$	1.1	2.0	Et_2O	17 : 1	
Bu_3SnH	2.4^{d}	40	110°C	3 : 1	72%^{c}

[a] two step yield; [b] crude GC shows product is 97% pure; [c] yield reflects intermediate diol isolated and purified; [d] used as solvent; [e] only diketone observed.

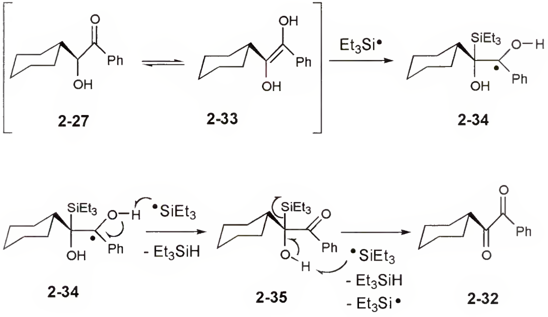
An interesting oxidation (**Scheme 2-6**) was noted for the thermal reaction between **2-27** and triethylsilane or triphenylsilane. Reduction of the ketone functionality was naturally expected, however, the only isolated product was that of dione **2-32** in 26% yield, when triethylsilane was used. Although this reaction is impractical for common use, it raises many questions about the reductive role of organosilanes and their intermediate pathways.



2-27 **2-32**

Scheme 2-6. Oxidation with Triethylsilane

A rationalization may be proposed (**Scheme 2-7**) which could explain this curious result. The enol tautomer of **2-27** is a conjugated gylcol **2-33**. It is well-known that silyl radicals react faster with olefins than carbonyls.[8, 17a] Triethylsilyl

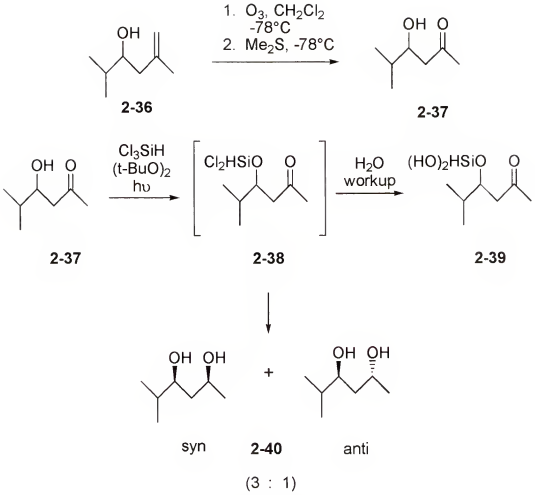


Scheme 2-7. Radical Oxidation Mechanism

radical can attack the double bond to give a 3° radical **2-34**, stabilized by delocalization via the phenyl ring. Of the silyl radicals studied, triethylsilyl radical is the most reactive towards olefin addition.[17a] Although trichlorosilane and TTMSS may hydrosilylate olefins as well, Chatgilialoglu explained that this is a reversible process, while triethylsilane adds irreversably.[17a] In work done by Giese and Kraus, a demonstration was made for chemoselective reactions on substrates containing both carbonyl and olefin functionalities. In this competitive reaction, the triethylsilyl radical preferred olefin addition whereas trichlorosilyl and TTMSS radicals added to the carbonyl.[4a, 8]

Abstraction of hydrogen by triethylsilyl radical produces the ketone **2-35**. With the introduction of another triethylsilyl radical, hydrogen atom abstraction from the alcohol may give the observed dione product **2-32** and triethylsilyl radical as a leaving group. More research needs to be done to investigate this reaction.

The reduction of β-hydroxyketones was approached next (**Scheme 2-8**). Ozonolysis of 2,5-dimethyl-3-hexen-3-ol (**2-36**) gave the β-hydroxyketone substrate **2-37**. When subjected to the standard free radical conditions with trichlorosilane, and intermediate β-silylether **2-38** forms. If the reaction is quenched too early with aqueous workup, a very polar dihydroxysilylether forms **2-39**. Allowing the reaction to proceed for 24 h gave a syn/anti diol **2-40** ratio of 3:1 in less than 20% yield. The reduced selectivity of the diastereomeric process was expected. It is well known that diastereoselective processes



Scheme 2-8. Reduction of β-hydroxyketones

become less effective when the directing group is located further from the reactive site.

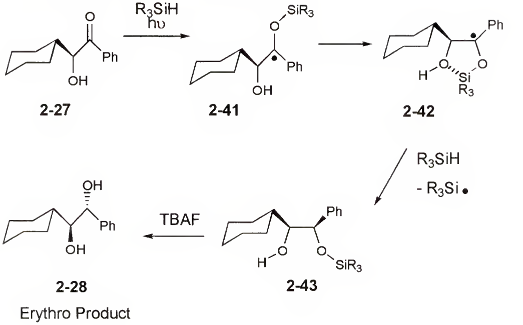
Mechanistic Study for Trichlorosilane Reduction

We believe that the electronic character of the substituents on silicon influence the degree of diastereoselectivity found in the product. It has been known for some time that electron-withdrawing groups on the silicon atom increase the rate of addition of organosilicon radicals to carbonyl groups and olefins.[4a] Tris(alkylthio)silanes, $(RS)_3SiH$,[24] are believed to provide electrophilic silyl radicals, due to the electronegativity of the sulfur and possible hyper-conjugation effects.[2]

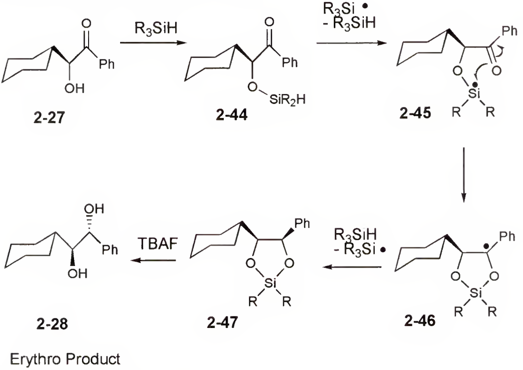
Two possible mechanisms may account for the diastereoselectivity seen in the reduction of **2-27**. In the case of mechanism A (**Scheme 2-9**, chelation control), a silyl ketyl **2-41** is initially formed by the reaction of **2-27** with trichlorosilane. It is believed that with electronegative chlorine substituents on silicon, the silicon atom in **2-41** becomes more electropositive in character. The more electron-poor the silicon atom in **2-41** becomes, the more susceptible silicon is to electron pair donation by oxygen. Hence, a tighter chelation with the α-hydroxy group will exist, to form intermediate **2-42**. This expected tight chelation gives rise to the high diastereomeric preference in the products, after **2-42** abstracts an H-atom from the silane reagent to give silylether **2-43**. After deprotection with TBAF, the main product **2-28** is conceived in its erythro form.

An alternate explanation (**mechanism B, scheme 2-9**) involves the initial formation of an α-silylether ketone **2-44**. It is known from the literature that the chlorine substituents on Cl_3SiH may be displaced by alcohols to form silylethers.[25, 26] Reaction of **2-27**, therefore, may produce silylether **2-44**. H-atom abstraction by a chain carrying radical could then form intermediate **2-45**. The electronegativity of the Si-atom substituents on **2-45** would be expected to have a profound effect on the silyl radical's electronic character. With chlorine

Mechanism A: Via Chelation Control



Mechanism B: Via bis-Silyl Ether



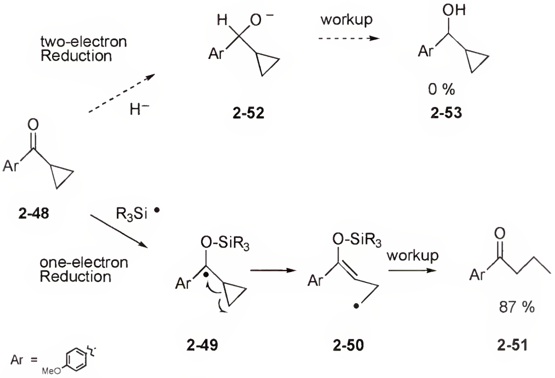
Scheme 2-9. Proposed Mechanisms

substituents (R = Cl), the silyl radical in **2-45** should be highly electrophilic. Bis-silylether radical **2-46** forms when the silyl radical attacks the electron-rich oxygen of the ketone. The five-membered ring provides a steric bias for stereoselective H-atom abstraction to produce bis-silylether **2-47**. Cleavage of the silicon with TBAF can then produce the erythro diol product **2-28** as expected.

We believe that TTMSS shows a very poor diastereomer ratio because the $SiMe_3$ substituents on silicon are less electron-withdrawing than chlorine, thus providing a weaker chelate intermediate **2-42** (**mechanism A**). Alternatively, it is unlikely for the trimethylsilyl substituents on TTMSS to be displaced by the alcohol to provide **2-44** (**mechanism B**). To our knowledge, no such reaction has been indicated in the literature. Finally, the sterically encumbered $Si(SiMe_3)_3$ may hinder the formation of either cyclic intermediate **2-42** or **2-46**.

In view of the evidence, it would seem that **mechanism B** is more likely correct. Considering that dichlorosilylether **2-38** was observed in the β-hydroxyketone example, this indicated that prior coordination of the silane reagent to the substrate had occurred. Experimentally, this is evidenced by noticing a vigorous bubbling when trichlorosilane is initially added to the alcohol substrate.

An experiment was carried out to determine whether trichlorosilane is reacting in the capacity of a free radical reducing agent (as trichlorosilyl radical) or as a hydride donor (H^-) toward the ketone functional group. In a similar study, it has been shown that TTMSS serves as a one-electron reducing agent.[8] **Scheme 2-10** displays the possible one- and two-electron reduction mechanisms of trichlorosilane with cyclopropyl-4-methoxyphenyl ketone (**2-48**). In the first case, a one-electron reduction of **2-48** would initially give intermediate silylketyl **2-49**, which would quickly open the cyclopropyl ring to provide trichlorosilyl enolether radical **2-50**. Intermediate **2-50** could then abstract a hydrogen atom from the silane reagent to propagate the radical process, and TBAF cleavage of the Si-O bond would yield 1-(4-methoxyphenyl)-1-butanone (**2-51**).[27]



Scheme 2-10. Mechanism Study with Trichlorosilane

The second case involves generation of a hydride atom from trichlorosilane, which could reduce **2-48** to the oxyanion **2-52** by a two-electron mechanism. This is unlikely, since it would require the formation of trichlorosilyl cation, which would be highly unstable on thermodynamic grounds. If **2-52** were formed, however, protanation during workup would provide cyclopropyl(4-methoxyphenyl)methanol (**2-53**). Under photochemical conditions, ketone **2-51** was formed in 87% yield, with no trace of alcohol **2-53** found. Kraus and Liras also provided supporting evidence for the radical mechanism, in their work on trichlorosilane-mediated intramolecular cyclization of enones.[8]

Conclusions

Silicon hydrides are increasingly becoming an attractive alternative to tin hydrides for many reasons. Silicon hydride reactions are much easier to work up, purification of products is often facile, and the silicon byproducts are more environmentally benign than the analogous tin compounds. An important advantage of the present synthetic method is that a single major, predictable diol diastereomer can be formed in high yield from an α-hydroxy ketone, using the inexpensive and readily available trichlorosilane.

Also, unlike the previous methods, the reaction is done using standard lab apparatus, not requiring sealed-tubes and high temperatures. Contrary to the established two-electron reducing agents, the reaction is carried out in non-basic media. The impressive selectivity of trichlorosilane seems to have a bright and promising future. The full potential of this method however, has not yet been established.

CHAPTER 3
CATALYTIC POLYMER-SUPPORT TIN HYDRIDE REDUCTIONS

Background

Polymer support for organic chemistry was established in the early 1970's.[28] The advantage of this developing chemistry is its ability to easily purify the products from excess reagents and byproducts. Typically, the substrate is mounted onto a resin (solid-support) with a spacer linking them (**Figure 3-1**). The reaction proceeds with a large excess of reagent, taking care not to stir too vigorously, or the resin (bead) will break apart. After the reaction is complete, the substrate-bound polymer support is washed of impurities and excess reagent. The product is then cleaved off of the support and isolated as a pure substance, filtering the resin for later use.

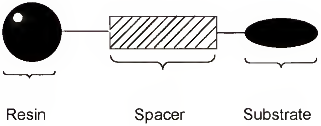
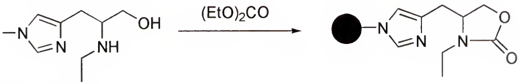


Figure 3-1. Design of a Polymer Support

The Merrifield and Wang resins, which are commercially available cross-linked polymers, have been typically used for polypeptide synthesis (**Scheme 3-1**).[29] During the past couple of decades, the use of solid-phase chemistry has

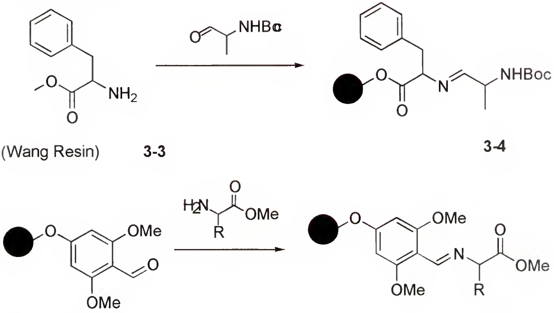
Urethane Formation



(2-Chlorotriphenyl-
methyl Resin) **3-1**

3-2

Imine Formation



(Wang Resin) **3-3**

3-4

(Merrifield Resin) **3-5**

3-6

Scheme 3-1. Literature Applications on Polymer Support

been applied to a variety of transformations, including: amide bond formation, aromatic substitutions, condensations, cycloadditions, diazotisations, enzymatic couplings, Grignard reactions, Michael additions, nucleophilic substitutions, olefinations, oxidations, reductions, protections/deprotections, and cleavages. Several reviews can be found in the literature that covers the broad scope of this methodology.[30]

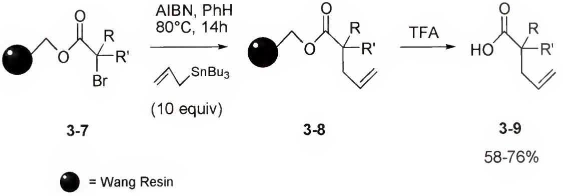
Despite the much-flaunted benefits associated with cross-linked polymer supports, several notorious drawbacks have been established. In most cases, the divinylbenzene crosslinked resins are not only expensive, but insoluble in organic media. This necessitates long reaction times and a large excess of reagent, wasting both time and money. Also, commercial resins are often found to have a very low percentage of reactive sites available (Wang Resin = 1.0-1.5 mmol OH^-/g of resin; Merrifield Resin = 1.0-1.5 mmol Cl^-/g of resin).[31] This means that for a prep-scale reaction to occur, a huge amount of expensive resin would be needed. Finally, monitoring a solid phase organic reaction is very difficult, where NMR and TLC are not useful.

A viable alternative is the use of soluble, non-crosslinked polymer supports. For peptide synthesis, it has been demonstrated that the rate of coupling reactions for soluble non-crosslinked polymers is of the same order of magnitude as traditional ‘wet chemistry’. This rate is a factor of 10^2 faster than the popular, insoluble crosslinked polymer methods.[32]

There are several other benefits connected to the use of non-crosslinked polystyrene supports. First of all, they are inexpensive and simple to prepare.

Secondly, the amount of reactive sites, Percent Functionality (**PF**) may be varied during synthesis, at the discretion of the researcher. Thirdly, most derivatives are soluble in commonly used organic solvents (EtOAc, benzene, $CHCl_3$, CH_2Cl_2, DMF, DMA and THF), which allows for faster reaction times and the ability to analyze reaction mixtures by ^1H NMR. Fourthly, these polymers are characteristically insoluble in MeOH or water, permitting for purification by crystallization of the product. Finally, the crystalline nature of these non-crosslinked polymers also allows for convenient handling of toxic reagents such as tin (vide infra).

It was the goal of this research to study the possibility of tin hydride radical reactions on solid support. Reports of one-electron reactions occurring on solid support are infrequent,[33] yet some research has been done with the use of organotin chemistry. Studies made by Sibi (**Scheme 3-2**) show intermolecular

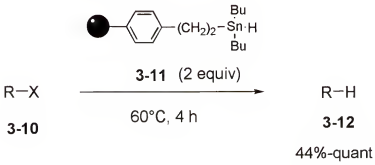


Scheme 3-2. Sibi's Tributylallyl Tin Reaction

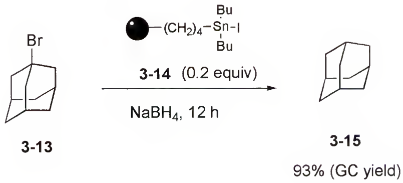
allylation of α-bromoesters, by the use of a modified substrate-bound Wang resin **3-7**.[34] Reaction of the resin **3-7** with 10 equiv of allyltributyl tin occurred at standard radical conditions, providing the alkylated ester **3-8**. After removal of tin impurities by washing the resin, hydrolysis with TFA provided the desired pure carboxylic acid **3-9**. Unfortunately, this methodology required the application of huge excesses of allyltributyltin and 3-4 equiv. of AIBN initiator.

It had occurred to us that creating a *reagent-bound* solid support would have several advantages. Once made, it could immediately be applied to

Neumann's Work



Dumartin's Work



Scheme 3-3. Literature Tin Polymers

several substrates. Higher overall yields are expected, because the extra steps to place the substrate onto (and eventually take off of) the polymer are avoided. The capacity of this methodology should also become broader, since substrates are no longer limited to only those which can bind to the resin.

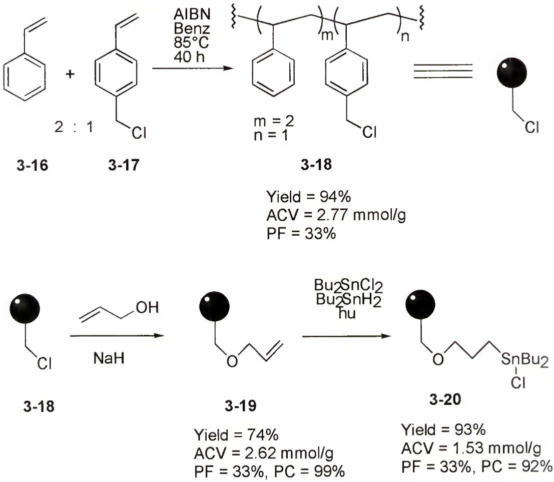
A goal was made of synthesizing a non-crosslinked tin polymer that could be used as an alternative to tributyltin hydride. Work by Neumann showed the possibility of creating a polymer-bound tin hydride reagent **3-11** that was effective at halogen atom abstraction (**Scheme 3-3**), but quantitative amounts (2 equiv) were necessary.[20b, 35] More recent research by Dumartin explored the tin pollution for a $NaBH_4$ reduction, catalyzed by a tin iodide polymer **3-14**.[36] Although his results proved only 0-34 ppm contamination, only one substrate **3-13** was explored and the yield was not based on isolated material.

Synthesis of Non-Crosslinked Dibutyltinchloride Polymer

A study was conducted to develop a soluble polymer with high tin content. Neumann reported synthesizing a polymer-support with a tin hydride equivalent of 1.5 mmol/g of polymer.[20b] He argued that a limit to the percent of active co-monomer was necessary, in order to prevent cross-coupling later in the synthesis. It was desired to improve the tin content, so that less polymer would be necessary to effect a reaction. The concerns raised by Neumann might be avoided by the judicious choice of a long spacer.

Several factors were taken into consideration when designing a suitable spacer. Dumartin pointed out that homobenzylic tin species might undergo β-elimination.[36] This process would both degrade the polymer and contaminate the reaction with tin byproducts. A stable, non-reactive spacer was needed that would withstand the conditions used in radical chemistry. The spacer also had to be able to incorporate the tin reagent onto the polymer support in high yields. It was decided to use an allylether spacer, due to its relative inertness, and attach the tin moiety by a hydrostannylation approach.

As shown in **Scheme 3-4**, a dibutyltin chloride polymer **3-20** was successfully synthesized by these protocols: a 2:1 mixture of styrene (**3-16**) and 4-vinylbenzyl chloride (**3-17**) were copolymerized under radical conditions to give a non-crosslinked random polymer **3-18** (see **Appendix**) in 94% yield. Theoretically, the reaction should inherently incorporate reactive sites at 33% of the polymer (Percent Functionality: (**PF**) = 33%), giving an Active Content Value (**ACV**) of 2.77 mmol/g. Displacement of the chlorine by allyl alcohol was accomplished in high yield (74%) to obtain an allylether polymer **3-19** (see **Appendix**) with an **ACV** of 2.62 mmol/g. Through ^{1}H NMR integration analysis, the incorporation of 4-vinylbenzyl chloride into the polymer backbone (**PF**) and the efficiency of SN_2 displacement [Percent Conversion: (**PC**)] were calculated to be 33% and 99%, respectively.[37] The method used by Neumann to photochemically hydrostannylate olefins with Bu_2SnH_2 and Bu_2SnCl_2 was successful.[20b] The target dibutyltin chloride polymer **3-20** (see **Appendix**) was isolated in 93% yield, with a **PC** of 92% and an **ACV** of 1.53 mmol/g.



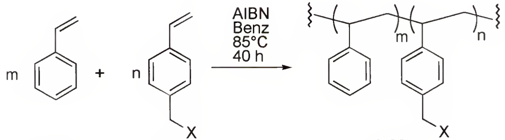
Yield = 94%
ACV = 2.77 mmol/g
PF = 33%

Yield = 74%
ACV = 2.62 mmol/g
PF = 33%, PC = 99%

Yield = 93%
ACV = 1.53 mmol/g
PF = 33%, PC = 92%

Scheme 3-4. Preparation of Tin Chloride Polymer

A relationship can be made between the Percent Functionality of a solid support, which ideally remains constant, and the Active Content Value, which changes as reactions occur on the polymer. As shown in **Scheme 3-5**, when 'm' moles of styrene (**3-16**) react with 'n' moles of *p*-substituted styrene (RX) **3-21**, a non-crosslinked copolymer **3-22** is formed. Based on the ratios of 'm' and 'n' used, and the respective molecular weights of the monomers, an expression can be derived (**eq 3-1**) for calculating the **ACV** in terms of mmol/g of polymer. It should be noted that as MW(RX) increases, the **ACV** decreases. Conversely,



Styrene **3-16**

RX **3-21**

3-22

$$\textbf{Active Content Value (ACV)} = \frac{(\mathrm{RX\%}) \bullet 1000\,\mathrm{mg}}{[\,(\mathrm{RX\%}) \bullet \mathrm{MW}_{(\mathrm{RX})}\,] + [\,(100\% - \mathrm{RX\%}) \bullet \mathrm{MW}_{(\mathrm{Sty})}\,]} \quad \textbf{(eq 3-1)}^{a}$$

$$\textbf{Percent Functionality (PF)} = \frac{[\,\mathrm{mmol(RX)} \bullet 100\% \bullet \mathrm{MW}_{(\mathrm{sty})}\,]}{1000\,\mathrm{mg} + \{\mathrm{mmol(RX)} \bullet [\,\mathrm{MW}_{(\mathrm{Sty})} - \mathrm{MW}_{(\mathrm{RX})}\,]\}} \quad \textbf{(eq 3-2)}^{b}$$

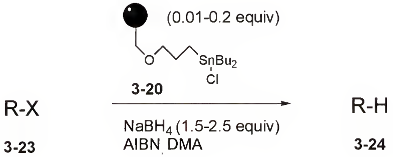
[a] ACV is in terms of mmol(RX) / gram of polymer;
[b] PF is with respect to mmol(RX%) in polymer

Scheme 3-5. Calculation of Active Site Values

if the **ACV** and molecular weights of the monomers are known, then the **PF** may be computed from **eq 3-2**.

Efficient Catalytic Reductions of Various Alkyl Halides

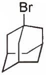
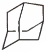
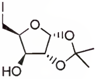
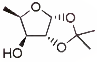
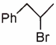
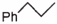
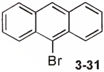
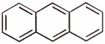
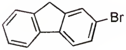
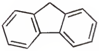
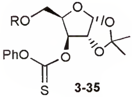
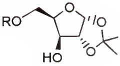
The dibutyltin chloride polymer **3-20** was tested for use as a catalyst in reducing alkyl halides and a thionocarbonate **3-23** with $NaBH_4$ (**Scheme 3-6**) to alkane products **3-24**. A variety of conditions were tried, to increase the yield and efficiency of the reaction. Typically, the alkyl halide **3-23** was dissolved in DMA and heated to 85°C with 0.1 equiv of **3-20** and 1.5 equiv of $NaBH_4$. After stirring for two hours and then cooling, the reaction solution could be directly applied to a column to isolate the pure alkane **3-24** without tin impurities.



Scheme 3-6. Catalytic Reductions

It can be seen from **Table 3-1** that the reductions of alkyl halides were highly successful. Yields ranging from 60% to 93% were obtained of isolated alkanes. Adamantane (**3-15**) was isolated in 60% yield by dehalogenation of adamantyl bromide (**3-13**), a 3° alkyl halide. When the same reaction was run

Table 3-1. Catalytic Reductions

Entry	Reagent	Catalyst (equiv)	$NaBH_4$ (equiv)	Time	Yield[a]	Product
1.	 **3-13**	0.2	2.5	2h	60% (99%)	 **3-15**
2.	 **3-25**	0.1	1.5	1h	85%	 **3-26**
3.	$CH_3(CH_2)_{10}CH_2I$ **3-27**	0.1	1.5	0.5h	88%	$CH_3(CH_2)_{10}CH_3$ **3-28**
4.	 **3-29**	0.01	1.5	6.5h[b]	93%	 **3-30**
5.	 **3-31**	0.1	2.5	2.5h	80%	 **3-32**
6.	 **3-33**	0.2	2.5	24h	74%[c]	 **3-34**
7.	 **3-35**	0.1	1.5	1.5h	47%	 **3-36**

[a] GC yield reported in parenthesis ( ). [b] TLC/GC shows rxn complete in 30min when 0.1 equiv cat. used. [c] Under similar conditions without the catalyst, GC showed only 30% conversion after 24h.

with decane as an internal standard, a GC yield of 99% was obtained (entry 1). Primary alkyl halides (entries 2 and 3; **3-25** and **3-27** resp) reacted the fastest, only requiring 0.5-1h for the reaction to complete.

In order to assess the catalyst's limitations, a reaction was run using only 0.01 equiv of the polymer **3-20** (entry 4). The dehalogenation of 2-bromo-1-phenylpropane (**3-29**), a 2° alkyl halide, was successfully completed in 6.5 h. Increasing the catalyst amount to 0.1 equiv afforded total conversion within 30 min, as determined by GC analysis.

Aryl halides **3-31** (entry 5) and **3-33** (entry 6) were also explored. Although reaction times were longer (2.5 h and 24 h resp), the isolated yields were very good, ranging from 74% to 80%. A comparison was made to appraise the efficiency of the catalyst at reducing 2-bromofluorene (**3-33**) to fluorene (**3-34**). Using 0.2 equiv of the polymer catalyst and 2.5 equiv $NaBH_4$, GC showed the reaction went to completion in 24 h. Under the exact same conditions, without use of catalyst **3-20**, only 30% conversion to product **3-34** occurred after the same amount of time. In all reactions, ^{13}C NMR and ^{1}H NMR analysis indicated no contamination by tin byproducts.

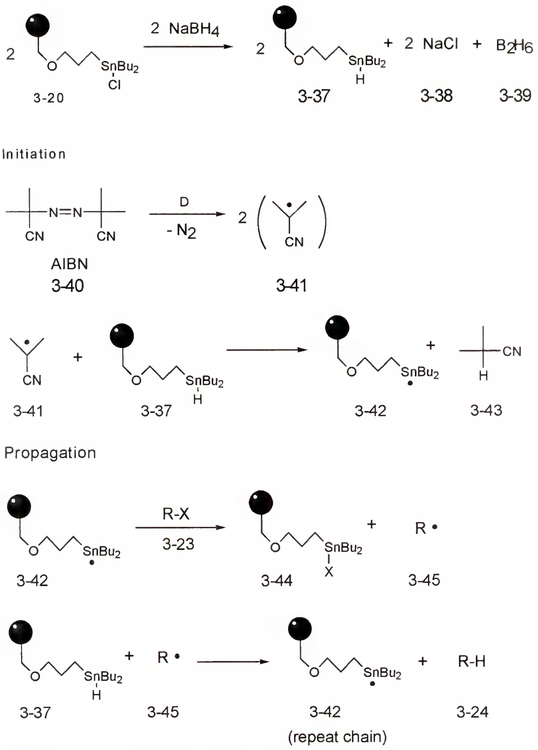
For the final example, an attempt was made at reducing a thionocarbonyl **3-35** to the alkane. Under standard conditions, deprotection occurred to give the free alcohol **3-36** in 47% isolated yield. Unfortunately, it seems that hydride attack on the thionocarbonyl was preferred over ketyl formation, which would have led to the desired product.

Mechanism of Reduction

In 1975 Corey presented his $NaBH_4$ mediated reduction of alkyl halides, catalyzed by tributyltin chloride.[13c] Our polymer-bound dibutyltin chloride catalyst is expected to function in the same manner as proposed by Corey. As seen in **Scheme 3-7**, the mechanism begins with the hydride attack on polymer **3-20** to give dibutyltin hydride polymer **3-37**, NaCl (**3-38**) and B_2H_6 (**3-39**). Radical initiation from AIBN (**3-40**) provides cyanoisoproply radical **3-41**. In the first propagation step, this radical abstracts hydrogen from **3-37**, producing a dibutyltin radical **3-42** and isopropylcyanide (**3-43**). The tin radical **3-42** can then efficiently abstract the halogen from alkyl halide **3-23** to yield dibutyltin halide **3-44** and alkyl radical **3-45**. Subsequent quenching of alkyl radical **3-45** occurs by abstracting a hydrogen atom from **3-37**, regenerating tin radical **3-42** and giving the desired alkane **3-24** as expected.

Conclusions

A new and highly effective catalyst was designed for $NaBH_4$ mediated reduction of alkyl halides. Primary, secondary, tertiary, and aryl halides were all successfully converted to simple alkanes, without noticeable byproducts and in high yields. One example of a thionocarbonyl did not deoxygenate under the conditions studied. The solid-support tin chloride catalyst showed an excellent increase in the rate of reaction, with very few milliequivalents necessary. The



Scheme 3-7. Mechanism of Reduction

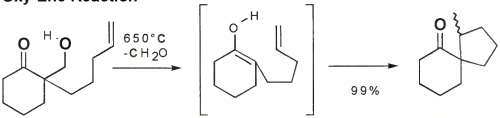
stable polymer showed no signs of degradation and allowed for facile purification of products, without contamination of tin residues. The simple and inexpensive design of the catalyst compliments its high yield of formation and productivity.

CHAPTER 4
CARBOMERCURATION CYCLIZATIONS OF ENONES USING TRIBUTYLTIN HYDRIDE

Background

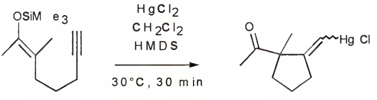
Since the advent of Conia's oxy-ene cyclizations[38] (**Scheme 4-1**), several variations have been introduced by the scientific community using organometallic chemistry.[39] Further advancement in this area was evolved by Druin and Conia, employing the cyclization of acetylenic carbonyl compounds

Oxy-Ene Reaction



4-1 **4-2** **4-3**

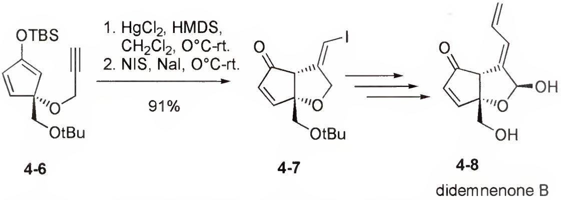
Carbomercuration



4-4 **4-5** quant.

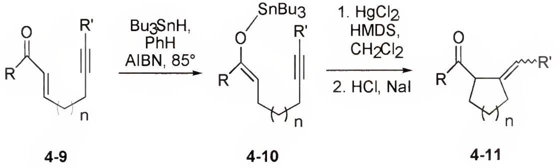
Scheme 4-1. Conia's Cyclizations

via their silyl enol ether derivatives **4-4**.[40] Notably, this intramolecular carbo-mercuration reaction is a little researched method, which takes advantage of electrophilic activation of a tethered acetylene to promote milder cyclization conditions than the original oxy-ene variety (**Scheme 4-1**). Proponents of this method have accomplished the synthesis of (+/-) erythrodiene and (+/-) didemnenones A and B (**4-8**) (**Scheme 4-2**).[41]



Scheme 4-2. Practical Application of Carbomercuration

The objective of this project was to develop a methodology, which may produce several unconjugated cyclic enones of type **4-11** in **Scheme 4-3**.



Scheme 4-3. Project Goal

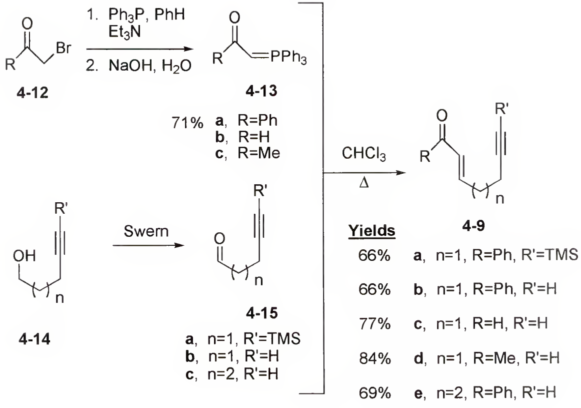
Preparation of such exo-ketones with a β,γ olefin is very difficult. Our new method would utilize simple enone precursors **4-9**, which would produce a tin enolate **4-10**, as a nucleophilic intermediate.

This new intramolecular carbomercuration has been successful, and will be reported herein. The new procedure employs the well-understood formation of allylic tin ketyls, which can lead to tin enolates **4-10**.[9b] This method generates, *in situ*, a precursor to mercury induced cyclization of the type mentioned above. These are the first known examples of tin enolates functioning in such a capacity.

Our method has an advantage over that of Druin and Conia, because the tin enolate **4-10** is generated under mild, neutral conditions. Also, the enolate regiochemistry is fixed, being determined by the conjugation at the α,β position. Conversely, Druin and Conia's route requires the formation of a silyl enol ether precursor, which is typically carried out in basic media and requires one side to be fully substituted (blocked) at the α-position to prevent a mixture of enolate regioisomers (**Scheme 1-11**).[42]

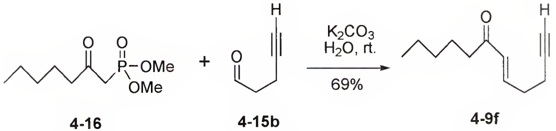
Synthesis of Enone Precursors

As seen in **Scheme 4-4**, the production of a variety of phosphorus ylides **4-13** and alkynals **4-15** proceeded under standard conditions.[43-45a] Several different unsaturated alkynone precursors **4-9a-e** were readily synthesized from



Scheme 4-4. Wittig Reactions

a Wittig reaction between the aldehyde **4-15** and phosphorus ylide **4-13** substrates in very good yields (66-84%).[46] A convenient aqueous mediated Horner-Wadsworth-Emmons reaction (**Scheme 4-5**) provided another precursor,



Scheme 4-5. Horner Wadsworth Emmons Reaction

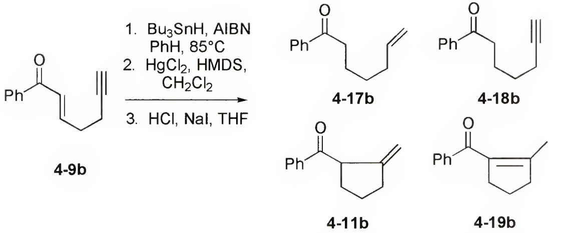
compound **4-9f** in 69% yield by the condensation of aldehyde **4-15b** with dimethyl(2-oxoheptyl)-phosphonate (**4-16**).[47]

Results of Carbomercuration Cyclizations

Scheme 4-3 illustrated the goal of converting the acyclic unsaturated alkynones **4-9** to cyclized products **4-11** utilizing tin enolate **4-10** and carbomercuration chemistry. An attempt to obtain a cyclized product from the disubstituted acetylene **4-9a** failed. Reduction of the α,β olefin occurred, indicating that the tin enolate had formed and was quenched upon workup. It is believed that the TMS group hindered the coordination of $HgCl_2$ to the alkyne, preventing its use as a kinetically viable electrophilic reactive site. This observation was supported by the literature.[40b]

Monosubstituted acetylenes were next explored, with mixed results. Aldehyde **4-9c** and methyl ketone **4-9d** precursors also gave only reduced products. It was noted by TLC monitoring that tin enolate formation proceeded poorly, giving several spots. The long chained ketone **4-9f** seemed to form a tin enolate sluggishly, but the cyclization did not proceed as expected. The phenyl ketone precursors **4-9b** and **4-9e** did form tin enolates well, and cyclized successfully.

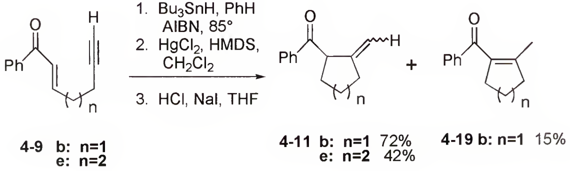
As shown in **Scheme 4-6**, depending on the reaction conditions, a variety of products could be formed. At first, an excess of tributyltin hydride (1.5-2 equiv, step 1) was used. Unfortunately, this allowed for hydrostannylation



Biproducts **4-17b, 4-18b** and **4-19b** can be avoided by changing reaction conditions.

Scheme 4-6. Early Results

product **4-17b** to compete with cyclization. Changing conditions to employ 1equiv of tributyltin hydride prevented this problem. Once the tin enolate was formed, if the carbomercuration step (step 2) was not allowed to proceed long enough, then uncyclized material **4-18b** was isolated in the workup. Longer reaction times for step 2 prevented this particular byproduct. Conjugated enone

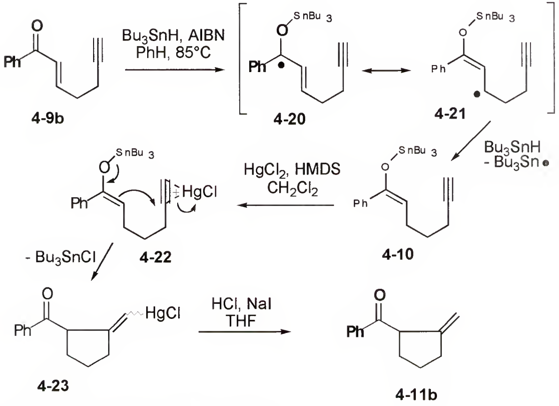


Scheme 4-7. Tin Enolate Carbomercurations

4-19b is the thermodynamic product that forms during protio-demercuration (step 3), which can be minimized by shorter reaction times in the acidic media.

After carefully changing reaction conditions to avoid byproducts, the desired product was maximized (**Scheme 4-7**). It was determined that alkynone **4-9b** gave two cyclized products, **4-11b** and **4-19b** in a ratio of 4.8:1, with an overall yield of 87%. From alkynone **4-9e**, only one cyclized product **4-11e** was isolated in 42% yield.

Proposed Mechanism



Scheme 4-8. Proposed Mechanism

Upon heating of the α,β-unsaturated ketone substrate **4-9b** with standard free radical tin conditions (**Scheme 4-8**), an allylic tin ketyl **4-20** is generated. The resonance structure, a tin enolate radical **4-21**, abstracts an H-atom from tributyltin hydride to yield a tin enolate **4-10** and a molecule of tributyltin radical. The reaction is then subjected to Mercury (II) Chloride, which oxidatively adds to the tethered acetylene to form intermediate **4-22**. This electron-deficient mercurium ion is then susceptible to attack by the adjacent electron-rich tin enolate, losing tributyltin chloride in the process. The resultant product is a vinylmercurial ketone **4-23**, separated by a cyclopentane (or hexane) ring. Subsequent demercuration with HCl and NaI affords the desired α-cyclo ketone **4-11b**.

Conclusions

An important advantage of the present synthetic strategy is that a single, predictable enolate regioisomer can be formed from an easily made enone precursor. Also, unlike the established method, the enolate is made under neutral, free radical conditions. Several competing byproducts may be avoided or minimized by the judicious use of reaction conditions. Pending further investigation, possible applications to form α-cyclo ketone products may include: carbo- and oxy-spirobicyclics, bridged bicyclics, fused bicyclics, and monocyclics. Our methodology has not been fully investigated and much more work has yet to be done. The broad scope of the tin enolate promoted carbomercuration seems to have a bright and promising future. The full potential of this method however, has not yet been established.

CHAPTER 5
SYNTHESIS OF MEDIUM RING BICYCLES AND LINEAR TRICYCLES VIA TIN KETYL RING OPENING OF [2+2] PHOTOADDUCTS

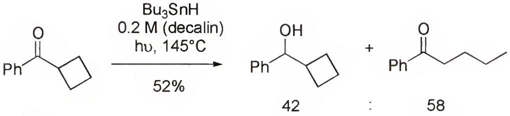
Background

Tin radical mediated opening of cyclopropyl rings is well known,[6, 48] yet the opening of cyclobutyl rings have been seldom studied in the literature. A tin ketyl opening of an adjacent cyclobutane ring from cyclobutylphenyl ketone (**5-1**) has been reported by Godet and Pereyre (**Scheme 5-1**).[49] The high temperatures used to affect this reaction (145°C), poor product ratios (reduction **5-2**/ring opening **5-3**; 42:58 resp), and the mediocre yields (52%) encouraged improvements in this area. Recently, radical fragmentation of cyclobutanes **5-4** to form medium ring fused carbocycles **5-5** was also explored by Crimmins.[50] His use of a thiocarbamate leaving group gave promising results (46-86% yield).

The employment of radical intermediates to undergo ring closure and ring contraction is also known. Studies by Winkler illustrate transannular radical cyclizations (**Scheme 5-2**).[51] His use of tributyltin hydride to abstract a halogen from the starting material **5-6** led to reactive intermediate **5-7**, which then underwent a 5-exo-trig cyclization to give **5-8**. Quenching of radical **5-8**, to give either cis **5-9a** or trans **5-9b**, resulted in bicyclic products. Ring contraction of

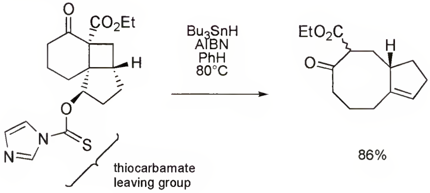
5-8 was also observed, to provide linear triquinane **5-10** (cis-anti-cis) and **5-11** (cis-syn-cis).

Godet and Pereyre's Work



5-1 **5-2** **5-3**

Crimmin's Work

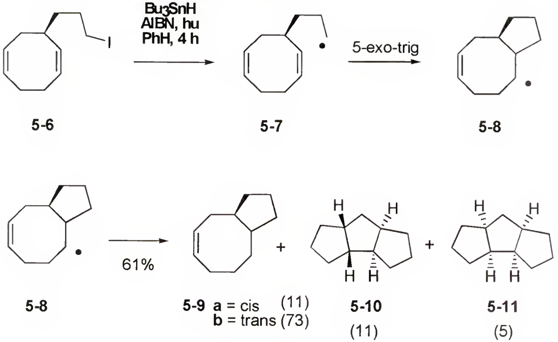


5-4 **5-5**

Scheme 5-1. Cyclobutane Ring Opening in the Literature

Lange also performed research into ring expansions, via cyclobutane opening. Initial work involved acid catalyzed carbocation processes.[52] Later, his group utilized the efficiency of tributyltin at cleaving iodoxanthates **5-12** to provide medium ring bicyclics **5-13** (**Scheme 5-2**) in a radical mechanism.[53]

Winkler's Research - Ring Contraction



5-6

5-7

5-8

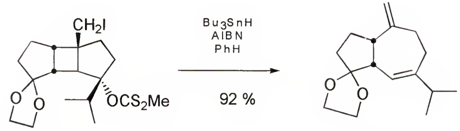
5-8

5-9 a = cis (11)
b = trans (73)

5-10
(11)

5-11
(5)

Lange's Research - Ring Expansion



5-12

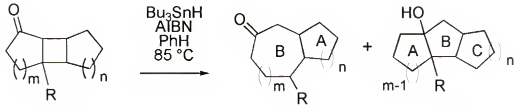
5-13

* Number in parenthesis ( ) indicate product ratios

Scheme 5-2. Ring Contractions From Literature*

To our knowledge, no research had been done on forming tin ketyls from ketone substrates, and their effect on ring expansion through cyclobutane moieties. Furthermore, no one has explored the possibility of radical ring contraction promoted by tin ketyl formation. The research presented in this chapter will address these issues.

Medium ring bicycles and linear tricycles have been formed in a unique ring-opening process, involving the use of tributyltin hydride (**Scheme 5-3**). Various tricyclic [2+2] photoadduct precursors **5-14** were used to react under free radical conditions, giving rise to either a medium ring system **5-15**, or a linear tricyclic product **5-16**.



5-14

5-15

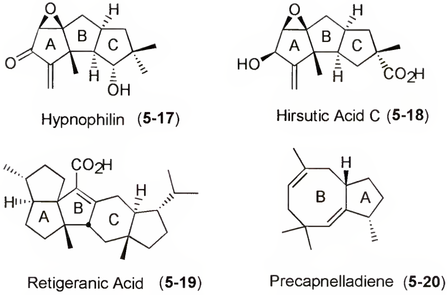
5-16

m = 1,2
n = 1,2
R = CO_2Me, Ph

(expected products)

Scheme 5-3. General Reaction

The existence of these two types of ring moieties has been found in nature (**Scheme 5-4**), and may be illustrated by several examples. Hypnophilin **5-17**, which displays activity against gram-positive and gram-negative bacteria, fungi, and yeasts, as well as antitumor activity, is an example of a linear tricyclic natural product.[54] Hirsutic acid C (**5-18**), isolated from the fungus *Stereum hirsutum*, has been shown to function as an antibiotic metabolite.[55] The well known retigeranic acid (**5-19**), which displays a pentacyclic sesterterpene moiety, has been isolated from various lichens found in the Himalayas.[56] Finally,



Hypnophilin (**5-17**)

Hirsutic Acid C (**5-18**)

Retigeranic Acid (**5-19**)

Precapnelladiene (**5-20**)

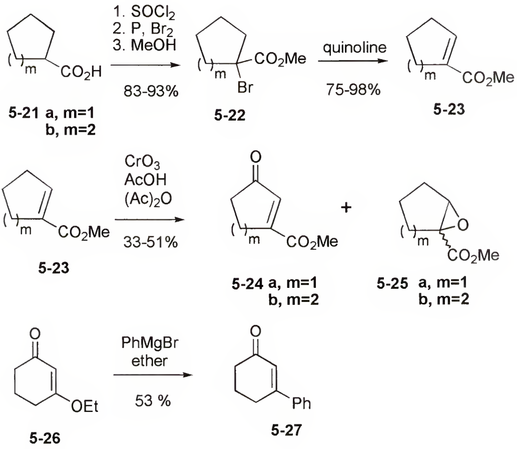
Scheme 5-4. Related Natural Products

precapnelladiene (**5-20**) is an example of a marine natural product which contains a fused bicyclic sesquiterpene skeleton.[57] Although many of these ring systems have been synthesized individually by various research groups,[58] they still present a challenge for creating a comprehensive methodology. Construction of a practical and expedient route to these important classes of compounds could potentially be a lucrative development.

Synthesis of [2+2] Photoadduct Substrates

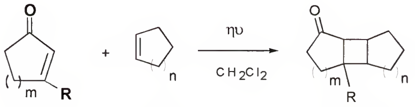
Several examples of the [2+2] photoadduct products exist in the current literature,[59] and entail facile formation from readily available compounds. Methyl-

3-oxo-1-cyclopentene-1-carboxylate (**5-24a**) and methyl-3-oxo-1-cyclohexene-1-carboxylate (**5-24b**) were prepared from cyclopentanecarboxylic acid (**5-21a**)



Scheme 5-5. Synthesis of Enones

and cyclohexanecarboxylic acid (**5-21b**) in a simple, four-step process (**Scheme 5-5**) employed by Lange.[60] The cyclic carboxylic acids were esterified and functionalized at the α-position **5-22** by the Hell-Volhard-Zelinski reaction, using thionyl chloride, red phosphorus, bromine, and methanol (83-93% yield).[61] Elimination to the alkene **5-23** was promoted by the use of quinoline (75-98% yield), followed by allylic oxidation (33-52% yield) with CrO_3 and acetic anhydride. Epoxidation of the olefin also occurred **5-25a,b**, giving a reduced yield of the desired ketoesters **5-24a,b**. Earlier, Sharpless had observed the possible formation of epoxides during Cr (IV) oxidations.[62] Finally, dihydroresorcinol ethyl ether (**5-26**) was reacted with phenyl magnesium bromide to provide 3-phenylcyclohex-2-en-1-one (**5-27**), in moderate yield (53%).[63]



5-24a,b
or **5-27**

5-28 a; n=1
b; n=2

5-14a-e

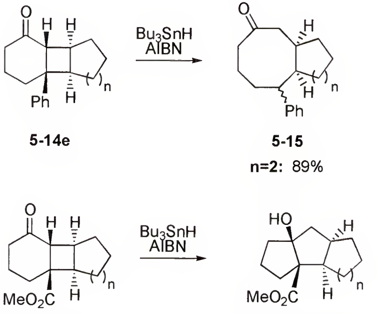
	Yield (%)	**anti/syn ratio**
5-14 a; R = CO_2Me, m=1, n=1:	92	6 : 1
b; R = CO_2Me, m=1, n=2:	93	-
c; R = CO_2Me, m=2, n=1:	86	9 : 1
d; R = CO_2Me, m=2, n=2:	95	7 : 4
e; R = Ph, m=2, n=2:	97	4 : 1

Scheme 5-6. Synthesis of Photoadducts

These conjugated cyclic ketoesters were then used in a [2+2] photoaddition with various cycloalkenes (**Scheme 5-6**). The yields from photolysis were found to be excellent (86-97%) and the method was very convenient, providing the cis-anti-cis diastereomers as the preferred products.

An improvement on Lange's method of synthesizing **5-14d**[53a] from cyclohexene (**5-28b**) was accomplished by the use of a methanol/t-butanol solvent system during photolysis, giving a yield of 95%. Using a variation of Lange's procedure,[52] similar results were obtained (86%) with much lower reaction times, for the formation of **5-14c** from cyclopentene (**5-28a**). Formation of **5-14a**, **5-14b** and **5-14e** was achieved with excellent results, using methods found in the literature.[52, 53a, 64 resp]

Ring Opening of Cyclohexanone Derivatives



5-14e

5-15
n=2: 89%

5-14 c; n=1
d; n=2

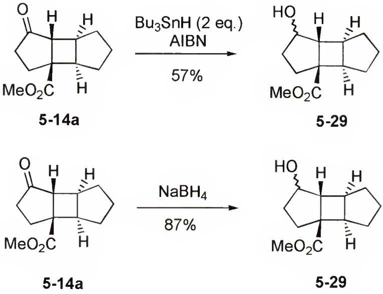
5-16 a; n=1: 68 %
b; n=2: 46 %

Scheme 5-7. Reaction with Cyclohexanone Systems

Depending on the β-substituent of the cyclohexanone ring system **5-14**, one of two products were formed when treated with tributyltin hydride. As can be seen from **Scheme 5-7**, the phenyl-substituted photoadduct **5-14e** allowed access to the medium ring bicyclic product **5-15** in excellent yield (89%). In contrast, the methyl ester-substituted photoadducts **5-14c,d** gave rise to the desired linear tricyclic products **5-16a,b** with fairly good yields (46-68%).

Results of Cyclopentanone Derivatives

Upon heating of the cyclopentanone ring system **5-14a** under standard free-radical conditions, the expected medium-ring bicyclic product did not form.



Scheme 5-8. Reaction with Cyclopentanone System

Instead, simple reduction of the ketone functionality occurred (**Scheme 5-8**) to provide an alcohol product **5-29** in 57% yield. This was confirmed by reducing the starting material with sodium borohydride and comparing the spectral data.

Proposed Mechanism

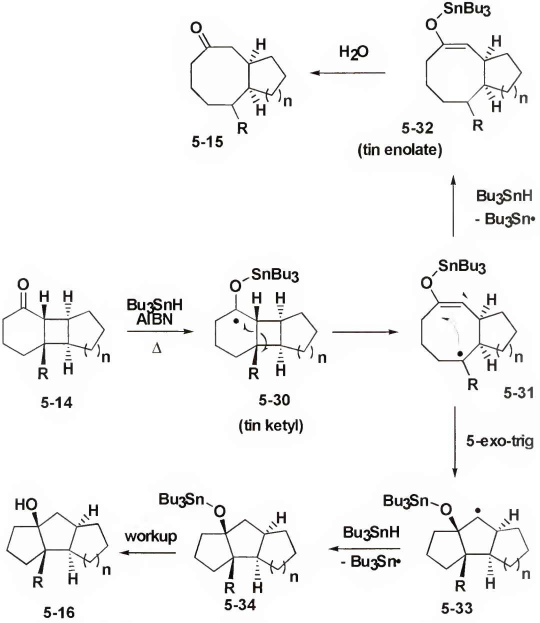
It is proposed that the desired bicyclic and tricyclic ring systems could be attained via the formation of a reactive tin ketyl intermediate **5-30**, as displayed in **Scheme 5-9**. Once the tin ketyl forms by heating the starting material **5-14** with tributyltin hydride, the adjacent cyclobutane ring may be opened to relieve ring strain. The subsequent tin enolate radical **5-31** may proceed through two separate pathways to provide two distinct products. Quenching of the radical species by abstraction of a hydrogen atom from tributyltin hydride gives a tin enolate **5-32** and regenerates the tributyltin radical. Further reduction occurs upon workup with water to yield the medium-ring bicyclic product **5-15**.

Alternatively, the tin enolate radical **5-31** can undergo a ring contraction, by intramolecular cyclization to obtain a secondary tin alkoxide radical **5-33**. This intermediate species may then abstract hydrogen from tributyltin hydride, catalyzing the process. The resulting tin alkoxide **5-34** is then converted into the desired linear tricyclic **5-16** by workup procedures.

It was interesting to note the variance in product outcome due to the identity of the β-substituent on the photoadduct. As shown in **Scheme 5-7**, when R=Phenyl **5-14e** the only product found was that of a medium-ring bicyclic **5-15**.

Alternatively for compounds **5-14c** and **5-14d** (R = CO_2Me), only the linear tricyclic products were made.

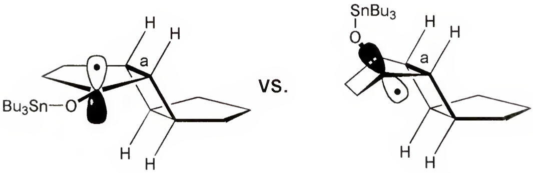
These observations are most likely explained by the function that the β-substituent plays when intermediate **5-31** is formed (**Scheme 5-9**). In the case



Scheme 5-9. Mechanism of Cyclohexanone Ring Opening

of the phenyl substituent, the carbon-centered radical is stabilized by conjugation throughout the aromatic ring and displays little electrophilic character. Therefore, the benzylic radical prefers hydrogen-atom abstraction than attack by the electron-rich tin enolate. Conversely for the ester substituent, the carbon-centered radical in **5-31** is essentially electron poor, due to the electron-withdrawing nature of the neighboring carbonyl. This electrophilic radical should preferentially attack the electron-rich olefin in a (5-exo-trig) manner.

There also exists a contrast in performance between the cyclohexanone and cyclopentanone precursors. This can be explained by an understanding of the inherent topological differences between these substrates. For facile



5-35

5-30

Cyclopentanone Ring Adduct

Less effective overlap prevents facile cyclobutane ring opening.

Cyclohexanone Ring Adduct

More effective overlap enables cyclobutane ring opening.

Figure 5-1. Comparison of Ring Systems

opening of the central cyclobutane ring, proper bond overlap must occur between the ketyl radical's p-orbital and the bond being broken. As shown in **Figure 5-1**, the cyclopentanone adducts are not as well situated, due to their fairly rigid ring system. Model studies show a nearly perpendicular alignment between the radical's p-orbital and the C-C bond of cyclobutane (bond 'a'). The result is that the initial tin ketyl **5-35** is simply quenched during workup and reduction of the ketone occurs.

In comparison, the cyclohexanone precursors exhibit better alignment (**Figure 5-1**) for bond construction. Upon ketyl formation, the flexibility of the cyclohexane ring allows for it to adopt a boat conformation **5-30**, whereby it obtains the necessary overlap with the adjacent C-C bond (labeled 'a'). This allows for the bond-making and bond-breaking process to occur, providing the ring-expanded intermediate.

Conclusions

Tributyltin hydride is an effective reagent for opening cyclobutane rings fused to cyclohexanones at C-2 and C-3. The reactions are carried out under neutral free-radical conditions and good to excellent yields are obtained. Both linear tricyclics and fused medium-ring bicyclics were formed, depending on the nature of a substituent group located at the β-bridgehead carbon. Analogous cyclopentanone substrates failed to perform as expected. The ketone functionality was reduced without ring expansion, most likely due to the poor orbital overlap of the radical and the cyclobutane ring.

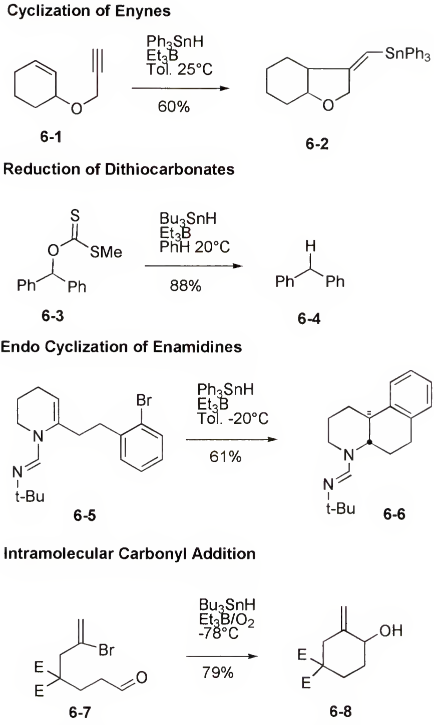
A variety of [2+2] photoadduct precursors can be synthesized in very high yields (86-97%), by an easy and convenient manner. An improvement in solvent systems was developed for the cycloadditions, giving higher yields and shorter reaction times for some substrates. As reported by other research groups, the photoadducts form with predominantly cis-anti-cis stereochemistry being favored, as expected for thermodynamic stability.

CHAPTER 6
LOW-TEMPERATURE REACTIONS OF TRIBUTYLTIN HYDRIDE

Background

A wide array of radical reactions involving tin and silicon hydrides is known in the literature. The primary generation of radical species is usually accomplished by photoinitiation or chemical initiation. A variety of chemical initiators are used, like AIBN and t-butylperoxide, which require specific activation temperatures (60-160°C) well above ambient temperature. The conditions for radical reactions with these common initiators have serious limitations.[65] Since the late 1980's, the development of a Et_3B-mediated initiation has allowed chemists to perform radical reactions at much lower temperatures (-78 to 25°C).[66] Often, this enabled better regio- and stereochemical control in organic transformations.[65b, 67]

Many research groups have exploited this new technology for a variety of purposes. As seen in **Scheme 6-1**, low-temperature addition of triphenyltin radical to alkyne **6-1** has allowed for cyclization to give vinyltin bicyclics **6-2**.[68a] Oshima and coworkers have also demonstrated Et_3B mediated reduction of dithiocarbonates **6-3** to alkanes **6-4**.[68b] Similar work by Barton utilizes diphenyl silane to reduce thiocarbonyl derivatives of alcohols.[68c] Low-temperature radical



Scheme 6-1. Et_3B **Mediated Radical Reactions**

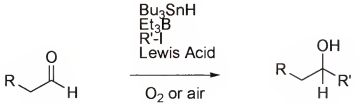
dehalogenation was accomplished by Hallberg, allowing for cyclization of enamidines **6-5** to polycyclic products **6-6**.[68d] Finally, intramolecular carbonyl **6-7** additions have been demonstrated in work done by Malacria, to form allylic alcohols **6-8**.[69]

Et_3B Initiated Intermolecular Alkylation of Aldehydes

Within the last decade, various research groups have examined the possibility of intermolecular additions of simple alkyl radicals with carbonyls. Conventional alkylation techniques involve organometallic reagents (alkyl lithiums, Grignard reagents, lithium dialkyl cuprates, etc.) which are plagued by high nucleophilicity and other drawbacks. Enolization of substrates with acidic α-hydrogens, possible interference by other functional groups, and the strong basicity of organometallic reagents are potential problems. Alkylation with carbon radicals may be able to avoid these dangers.

Sibi showed that 1,4-conjugate addition with alkyl radicals and chiral oxazolidinones were feasible,[70] while Naito provided a means for carbon radical 1,2-addition to aldoxime ethers.[71] To our knowledge, the literature is has no precedent for a convenient methodology which allows simple alkyl radical addition to aldehydes. The focus of our research has led us to explore a Lewis acid promoted, low temperature radical addition (**Scheme 6-2**). Using triethylborane/O_2 initiation techniques, an attempt was made to react alkyl halides (R'-I) with an aldehyde substrate **6-9**, to give 2° alcohol products **6-10**.

Develop methodology for radical alkylation of aldehyde

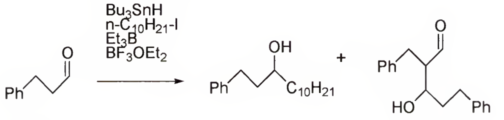


6-9 **6-10**

Scheme 6-2. Project Goal

As seen in **Table 6-1**, hydrocinnimaldehyde (**6-9**) was used as a substrate to be alkylated by iododecane. A variety of conditions were tried, in order to maximize the yield of alcohol product **6-10**. An aldol byproduct **6-11** was also formed in the course of the reaction. Under the radical conditions studied in entry 1, the reaction did not progress without a Lewis acid (BF_3OEt_2) being

Table 6-1. Radical Alkylation of Activated Aldehyde



6-9 **6-10** **6-11**

				Yields	
Entry	Conditions	Lewis Acid	Temp	6-10	6-11
1	dry air	-	-15 to 0°C	0 %	0 %
2	ambient	BF_3OEt_2	r.t.	0 %	only pdt
3	dry air	BF_3OEt_2	-20 to 0°C	28 %	26 %
4	dry air	BF_3OEt_2	-78 to 0°C	32 %	16 %

present. At higher temperatures (rt, entry 2) the main product was from aldol addition **6-11**, while at lower temperatures (-78°C, entry 4) the desired alcohol was predominant (**6-10/6-11**: 32%/16% yield).

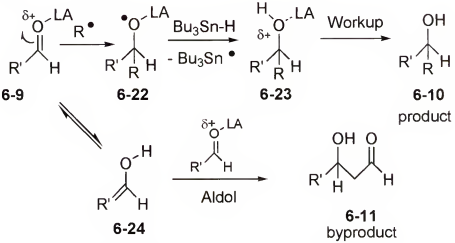
1. Initiation:

$$\underset{\textbf{6-12}}{Et_3B} + \underset{\textbf{6-13}}{O{=}O} \longrightarrow \underset{\textbf{6-14}}{Et^\bullet} + \underset{\textbf{6-15}}{Et_2B\text{-}O\text{-}O^\bullet}$$

$$\underset{\textbf{6-16}}{Bu_3Sn\text{-}H} + \underset{\textbf{6-14}}{Et^\bullet} \longrightarrow \underset{\textbf{6-17}}{Bu_3Sn^\bullet} + \underset{\textbf{6-18}}{Et\text{-}H}$$

2. Propagation:

$$\underset{\textbf{6-17}}{Bu_3Sn^\bullet} + \underset{\textbf{6-19}}{R\text{-}X} \longrightarrow \underset{\textbf{6-20}}{Bu_3Sn\text{-}X} + \underset{\textbf{6-21}}{R^\bullet}$$



Scheme 6-3. Proposed Mechanism

The mechanism (**Scheme 6-3**) of radical initiation with Et_3B and molecular oxygen is well known from the early work of H.C. Brown.[72] In the initiation step, triethylborane (**6-12**) reacts with oxygen (**6-13**) to form ethyl radical (**6-14**) and diethylboraneperoxy radical (**6-15**). H-atom abstraction from tributyltin hydride (**6-16**) by the highly reactive **6-14** generates tributyltin radical (**6-17**) and ethane (**6-18**). The propagation step begins when **6-17** undergoes halogen-atom abstraction from the alkyl halide **6-19**, yielding a molecule of tributyltin halide (**6-20**) and alkyl radical **6-21**. Prior coordination of the carbonyl substrate **6-9** with the Lewis acid allows for C-C bond formation with the alkyl radical **6-21**, giving an oxygen-centered radical intermediate **6-22**. H-atom abstraction from tributyltin hydride furnishes alcohol precursor **6-23**, and regenerates tributyltin radical (**6-17**). Subsequent workup of **6-23** with water yields the desired 2° alcohol **6-10**.

An alternate pathway can easily explain the formation of the aldol by-product **6-11**. The Lewis acid-activated aldehyde **6-9** has an enol tautomer **6-24**, as seen in **Scheme 6-3**. This reactive intermediate may undergo aldol addition with another activated aldehyde **6-9** to form byproduct **6-11**.

Conclusions

New novel, low-temperature radical reactions have been developed employing Et_3B/O_2 as the initiator and tributyltin hydride as the reagent. For the first time, C-C bond formation by simple alkyl radical addition to an activated aldehyde was discussed. The expected secondary alcohol product was isolated and despite low yields, several reaction parameters could be changed to possibly enhance the product outcome.

CHAPTER 7
EXPERIMENTAL

General Methods

A 450 watt (350nm) Hanovia mercury lamp was used for photochemical reactions, run in pyrex test tubes sealed with septa. Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer and are reported in wave numbers (cm^{-1}). ^1H Nuclear magnetic resonance spectra were recorded on a Varian VXR-300 (300 MHz) and a Varian Gemini-300 (300 MHz). ^{13}C NMR spectra were recorded at 75 MHz on the same spectrometers. Chemical shifts are reported in ppm downfield relative to tetramethylsilane as an internal standard. All mass spectroscopy was performed by the Mass Spectroscopy Service at the University of Florida Department of Chemistry. Elemental analysis was performed by either the Elemental Analysis Service at the University of Florida department of Chemistry or by Atlantic Microlab Inc. in Norcross, GA. All reactions were run under an inert atmosphere of argon using clean, oven dried reaction apparatus. All yields reported refer to isolated material determined to be pure by NMR spectroscopy and thin layer chromatography (TLC). Solvents and reagents were distilled under inert atmospheres.

Experimental Procedures

trans-4-t-butyl-1-tris(trimethylsilyl)siloxycyclohexane (2-24)

A solution of 4-t-butylcyclohexanone (**2-17**) (100 mg, 0.649 mmol) and t-butylperoxide (**2-19**) (60 μL,0.33 mmol) in TTMSS (241 μL, 0.779 mmol) was stirred for 10.5 hrs under hυ conditions. Excess reagent was removed by reduced pressure and the crude silylether was purified by flash chromatography through silica gel. The pure colorless oil **2-24** was collected (263 mg, 95%). ^{1}H NMR($CDCl_3$) δ:0.20(s, 27H), 0.85(s, 9H), 0.91-1.26(m, 5H), 1.68-1.96(m, 4H), 3.15(m, 1H); ^{13}C NMR($CDCl_3$)δ:0.39, 1.75, 4.41, 25.92, 27.71, 32.26, 36.25, 47.29; IR cm^{-1}: 1244.3, 1079.5, 838.0; HRMS(CI) calcd for $C_{19}H_{46}OSi_4$ (M+1) 403.2704, found 403.2731.

trans-4-t-butylcylclohexan-1-ol (2-18)

To a solution of 4-t-butylcyclohexanone (**2-17**) (100 mg, 0.649 mmol) in EtOH (5 mL, 0.13M), was added $NaBH_4$ (25 mg, 0.65 mmol). The solution was stirred at rt. for 1.5 hrs. After evaporation of solvent, the product was diluted with ether and extracted with water, then brine. Concentration of the ether layers provided a white solid **2-18** in 85:15 ratio of trans/cis resp. mp=62-66°C.

The following general procedure is representative for reduction with the tri-n-butyltin and silicon hydrides: Silylether intermediates were prepared as described above (for **2-24**), using the appropriate hydride reagent and the conditions outlined in **Table 2-1**. The crude product was then diluted with 3-5 mL of ether and 1-2 mL of a 1M solution of TBAF in THF was added at rt (with the exception of the tri-n-butyl hydride reaction, which was chromatographed directly). The solution was stirred for 1 h, then diluted with ether and extracted with H_20 then brine. After drying the ether layers with Na_2SO_4 and solvent removal, column chromatography provided the mixture of trans/cis 4-t-butylcylclohexan-1-ol (**2-18**) in the reported ratios. (**2-18**) trans: ^{1}H NMR($CDCl_3$) δ:0.85(s, 9H), 0.90-1.64(m, 6H), 1.71-1.87(m, 2H), 1.95-2.07(m, 2H), 3.52(m, 1H); ^{13}C NMR($CDCl_3$)δ:25.55, 27.60, 32.23, 36.00, 47.13, 71.12; IR(KBr)cm^{-1}: 1066.4, 1364.0, 1464.6, 3276.5; HRMS(CI) calcd for $C_{10}H_{20}O$ (M-OH) 139.1487, found 139.1487.

2-Cyclohexyl-2-hydroxy-1-phenylethanone (2-27)

The procedure described by J. A. Schreier was followed:[23] To a solution of 1-magnesium bromide ethenyl benzene (**2-26**) (6.6 mmol in 8.5 mL of THF) was added cyclohexane aldehyde (**2-25**) (0.93 g, 6.6 mmol) dropwise at 0°C. After complete addition the reaction was warmed to rt and stirred for 1 h. The reaction was quenched with NH_4Cl (aq, sat), washed with brine and dried over Na_2SO_4. removal of the solvent under vacuum yielded a yellow oil (1.43 g). The crude oil was dissolved in CH_2Cl_2 (70 mL) and subjected to ozone at -78°C until the solution turned blue. Dimethyl sulfide (1 mL) was added and the solution was warmed to rt. The solution was washed with water and brine, then dried with Na_2SO_4. Removal of the solvent under reduced pressure gave a yellow oil. Crystallization of the oil from methanol provided **2-27** as a white solid (1.22 g, 85%) mp = 89-90°C. ^1H NMR($CDCl_3$)δ:0.90-1.86(m, 11H), 3.61(d, 1H, J=6.6 Hz), 4.95(dd, 1H, J=6.6, 2.2 Hz), 7.42-7.95(m, 5H); ^{13}C NMR($CDCl_3$)δ:24.8, 25.8, 26.5, 30.3, 42.6, 77.3, 128.5, 128.9, 133.8, 134.3, 202.2; IR(KBr)cm^{-1}: 1108.4, 1450.1, 1677.6, 3417.6; HRMS(CI) calcd for $C_{14}H_{18}O_2$ (M+1) 219.1385, found 219.1387; Anal. calcd. for $C_{14}H_{18}O_2$: C, 77.03%; H, 8.31%. Found: C, 76.83%; H, 8.32%.

2-Cyclohexyl-2-phenyl-1,2-ethanediol (2-28, 2-29)

The following procedure is representative: In a small pyrex test tube, a solution was made of 2-cyclohexyl-2-hydroxy-1-phenylethanone (**2-27**) (100 mg, 0.459 mmol) with trichlorosilane (0.19 mL, 1.8 mmol). The vessel was sealed with a septum cap, tied with wire. The reaction was stirred under hυ overnight, excess silane reagent removed under reduced pressure, and then worked up with TBAF (as shown for **2-18** above). The solution was diluted with ether, extracted with water and brine, dried with Na_2SO_4, then the solvent was removed under reduced pressure. After column chromatography, 66 mg (65 %) of the diol mixture **2-28/2-29** was collected as a white solid, mp = 93-103 °C.

For reduction with other hydrides: See **Table 2-2** for conditions. After reduction with $LiAlH_4$, an LAH quench solid ($Na_2SO_4 \cdot 10H_2O$ with Celite, 1:1) was added to the solution slowly at 0 °C. The solid byproduct was filtered off and rinsed well with ether. The ether filtrate was then evaporated to give the crude diol product, which may be purified by flash chromatography. **2-28 erythro**: ^1H NMR($CDCl_3$)δ:1.00-1.48(m, 6H), 1.55-1.98(m, 6H), 2.43(s, 1H), 3.58(t, 1H, J=5.6 Hz), 4.71(d, 1H, J=5.6 Hz), 7.20-7.43(m, 5H); ^{13}C NMR($CDCl_3$)δ:25.86, 26.08, 26.39, 27.32, 29.95, 39.11, 74.69, 78.92, 127.28, 128.00, 128.42, 140.88; IR(KBr)cm^{-1}: 699.1, 755.8, 1012.7, 1377.0, 1452.5, 3362.0; HRMS(CI) calcd for $C_{14}H_{20}O_2$ (M+1) 221.1542, found 221.1542.

2-29 threo: ^1H NMR($CDCl_3$)δ:1.00-1.48(m, 6H), 1.55-1.98(m, 6H), 2.43(s, 1H), 3.41(t, 1H, J=6.0 Hz), 4.63(d, 1H, J=6.0 Hz), 7.20-7.43(m, 5H); ^{13}C NMR ($CDCl_3$)δ:25.93, 26.17, 26.27, 27.05, 30.09, 52.76, 74.16, 79.85, 126.48, 127.63, 128.27, 141.81; IR(KBr)cm^{-1}:699.1, 755.8, 1012.7, 1377.0, 1452.5, 3362.0; HRMS(CI) calcd for $C_{14}H_{20}O_2$ (M+1) 221.1542, found 221.1542.

Cis and trans acetonides (2-30, 2-31)

The crude mixture of diols **2-28** and **2-29** was dissolved in 6 mL of reagent grade acetone. Next, 2 mL 2,2-dimethoxypropane and a catalytic amount of p-TsOH was added, stirring at rt. for 6-8 hrs. The solvent was then removed by reduced pressure and the crude product was diluted with ether. After extracting with Na_2CO_3 (sat.) and brine, ether layers were dried with Na_2SO_4 then the solvent was evaporated to give the desired acetonides **2-30** and **2-31** as a colorless oil, in the ratios indicated in **Table 2-2**.

2-30 cis: ^{1}H NMR($CDCl_3$) δ:1.05-1.85(m, 17H), 4.03(dd, 1H, J=9.3, 6.6 Hz), 5.04(d, 1H, J=6.3 Hz), 7.20-7.42(m, 5H); ^{13}C NMR($CDCl_3$)δ:24.90, 25.28, 25.40, 26.30, 27.01, 28.85, 29.85, 37.72, 80.44, 83.19, 107.73, 127.70, 127.88, 128.23, 138.76; IR (KBr)cm^{-1}: 700.1, 757.1, 1051.2, 1217.3, 1370.4, 1450.5, 1702.2, 3360.4 (br); HRMS(FAB) calcd for $C_{17}H_{24}O_2$ (M-1) 259.1698, found 259.1683.

2-31 trans: ^{1}H NMR ($CDCl_3$) δ:1.05-1.85(m, 17H), 3.71(dd, 1H, J=8.4, 5.1 Hz), 4.73(d, 1H, J=8.4 Hz), 7.20-7.42(m, 5H); ^{13}C NMR($CDCl_3$)δ:26.01, 26.18, 26.35, 27.19, 27.26, 28.26, 30.00, 39.37, 80.89, 87.10, 108.33, 127.46, 128.15, 128.46, 138.78; IR (KBr)cm^{-1}: 700.1, 757.1, 1051.2, 1217.3, 1370.4, 1450.5, 1702.2, 3360.4; HRMS(FAB) calcd for $C_{17}H_{24}O_2$ (M-1) 259.1698, found 259.1683.

2-Cyclohexyl-2-phenyl-1,2-ethanedione (2-32)

A soln. of **2-27** (100 mg, 0.459 mmol) in triethylsilane (0.29 mL, 1.8 mmol) with t-butylperoxide (**2-19**) (0.084 mL, 0.46 mmol) was stirred at 110°C for 24 hrs. After typical TBAF workup, column chromatography provided 26 mg (26%) of pure **2-27**. ^{1}H NMR($CDCl_3$)δ:1.09-2.01(m, 10H), 3.06(m, 1H), 7.47(m, 2H), 7.261(m, 1H), 7.90(m, 2H); ^{13}C NMR($CDCl_3$)δ:25.32, 25.76, 27.22, 45.92, 128.84, 129.90, 132.59, 134.53, 194.23, 206.07; IR(KBr)cm^{-1}:3063.9, 1708.0, 1673.4, 1449.6, 915.2; HRMS(EI) calcd for $C_{14}H_{16}O_2$ (M^+) 216.1150, found 216.1148.

4-Hydroxy-5-methyl-2-hexanone (2-37)

A solution of **2-36** (20 g, 0.16 mol) in CH_2Cl_2 (520 mL, 0.3M) was made and subjected to ozone at -78°C until the solution turned blue. Dimethyl sulfide (137 mL) was added and the solution was warmed to rt. The solution was washed with water and brine, then dried with Na_2SO_4. Removal of the solvent under reduced pressure gave a tan oil. Purification of the crude material by column chromatography gave pure **2-37** (5.67 g, 28%). ^1H NMR($CDCl_3$) δ:0.92(t, 6H, J=6.3 Hz), 1.67(M, 1H, J=6.9, 6.6, 6.0 Hz), 2.20(s, 3H), 2.56(m, 2H), 3.43(s, br, 1H), 3.81(m, 1H); ^{13}C NMR($CDCl_3$)δ:17.3, 18.0, 30.4, 32.9, 46.9, 71.9, 209.7; IR(neat)cm^{-1}: 1709.3, 3448.2.

4-(dichlorohydrosiloxy)-5-methyl-2-hexanone (2-38)

A solution was made of **2-37** (100 mg, 0.769 mmol) and Cl_3SiH (417 mg, 0.31 mL, 3.08 mmol). The solution was stirred at 40ºC for 16 h, after which TLC showed the reaction was mostly complete. Crude reaction solution was applied directly to column, and silylether **2-38** was isolated pure (8 mg, 5%). It is believed that the product **2-38** bound to the silica gel column. ^1H NMR ($CDCl_3$)δ:0.97(dd, 6H, J=15.8, 6.8 Hz), 1.58(s, 1H), 1.94(m, 1H), 2.19(s, 3H), 2.67(dd, 1H, J=16.5, 3.8 Hz), 2.91(dd, 1H, J=16.5, 9.3 Hz), 4.29(dt, 1H, J=9.3, 4.2 Hz); ^{13}C NMR($CDCl_3$)δ:17.2, 19.6, 30.7, 34.0, 49.0, 63.3, 205.3.

Syn and anti 5-methyl-2,4-hexanediol (2-40)

A solution was made of **2-37** (100 mg, 0.769 mmol), t-butylperoxide (225 mg, 0.3 mL, 1.54 mmol), and Cl_3SiH (417 mg, 0.31 mL, 3.08 mmol). Reaction irradiated for 24 h then excess Cl_3SiH removed by vacuum. Solution diluted with ether and TBAF (1.08 mL, 1.08 mmol) added. Reaction stirred for 2 h, then extracted with water and brine. After drying ether layer with Na_2SO_4 and removal of solvent, the diol mixture **syn/anti 2-40** was collected (28 mg, 28% yield). GC showed syn/anti ratio to be 3:1, respectively.

syn isomer: ^{1}H NMR ($CDCl_3$)δ:0.91(dd, 6H, J=13.1, 6.6 Hz), 1.23(d, 3H, J=6.3 Hz), 1.40-1.76(m, 3H), 3.51-3.69(m, 3H), 4.12(m, 1H); ^{13}C NMR($CDCl_3$) δ:17.9, 18.5, 23.3, 33.6, 41.1, 65.1, 73.4; IR(neat)cm^{-1}: 1372.8, 1465.1, 3352.8 (br); HRMS(CI) calcd for $C_7H_{17}O_2$ (M+1) 133.1229, found 133.1277.

anti isomer: ^{1}H NMR ($CDCl_3$)δ:0.91(m, 6H), 1.22(d, 3H, J=6.3 Hz), 1.40-1.85(m, 3H), 3.64(m, 3H), 4.04(m, 1H); ^{13}C NMR($CDCl_3$) δ:17.5, 18.1, 24.1, 34.1, 40.8, 69.2, 77.8; IR(neat)cm^{-1}: 1326.0, 1373.2, 1466.2, 3353.5; HRMS(CI) calcd for $C_7H_{17}O_2$ (M+1) 133.1229, found 133.1277.

1-(4-methoxyphenyl)-1-butanone (2-51)

A soln. of cyclopropyl-4-methoxyphenyl ketone (**2-48**) (100 mg, 0.568 mmol) in trichlorosilane (0.58 mL, 5.7 mmol) with t-butylperoxide (**2-19**) (0.42 mL, 2.3 mmol) was stirred under hυ lamp for 3 d. Additional trichlorosilane (0.58 mL) and **2-19** (0.42 mL) were added and reacted under hυ for 3 d longer, after which TLC and GC indicated the reaction had gone to completion. Excess trichlorosilane was removed by reduce pressure, then the crude oil was diluted with ether. The ether was extracted with water and brine, dried with Na_2SO_4, then evaporated by vacuum. Column chromatography of the crude product provided 88 mg (87%) of pure **2-51** as a yellow oil. Spectral data for **2-51** agreed with values found in the literature.[27] ^{1}H NMR($CDCl_3$)δ:0.91(t, 3H, J=7.2 Hz), 1.67(sextet, 2H, J=7.2 Hz), 2.80(t, 2H, J=7.2 Hz), 3.76(s, 3H), 6.83(d, 2H, J=8.7 Hz), 7.85(d, 2H, J=8.7 Hz); ^{13}C NMR($CDCl_3$)δ:13.69, 17.77, 39.93, 55.17, 113.42, 130.03, 163.10, 198.71; IR(KBr)cm^{-1}:833.3, 1031.1, 1170.8, 1218.5, 1260.0, 1308.3, 1365.2, 1419.7, 1462.9, 1510.1, 1600.7, 1676.3; HRMS(EI) calcd for $C_{11}H_{14}O_2$ (M^+) 178.0994, found 178.0993.

p-Chloromethyl Polystyrene (3-18)[32]

To a solution of styrene (**3-16**) (15.9 g, 17.5 mL, 153 mmol), 4-vinylbenzyl chloride (**3-17**) (90%, 13 g, 77 mmol), and benzene (50 mL) was added AIBN (0.122 g, 0.74 mmol). The solution was then degassed with a stream of argon and heated to 80°C in an oil bath. After a reaction time of 40 h, the solution was cooled to rt and then poured into methanol (250 mL). Subsequent vacuum filtration onto a Büchner funnel and washing with methanol yielded the p-chloromethyl polystyrene polymer **3-18** (25.93 g, 94%) as a white solid (PF = 33%, ACV = 2.77 mmol/g). ^{1}H NMR ($CDCl_3$)δ: 0.90-2.30 (m, 9H), 4.51 (m, 2H), 6.00-7.50 (m, 14H). The integrations of the NMR were utilized to determine a Cl-CH_2- content of 33%.

p-Methyl allylether polystyrene (3-19)

Mineral oil was removed from NaH (60%, 0.73 g, 30 mmol) with pentanes. Dimethylacetamide (DMA) (5 mL) was added to the NaH under a stream of argon. At 0°C, allyl alcohol (1.76 g, 2.08 mL, 30.3 mmol) was added dropwise to the NaH mixture. Upon completion of the addition, the solution was stirred for 1h. Meanwhile, **3-18** (2.0 g, 5.5 mmol/g) was dissolved in DMA (6 mL). The polymer solution was then added to the allyl alcohol via cannula at 0°C. After stirring at room temperature for 24h, the solution was poured into vigorously stirring cold methanol (-40°C). Subsequent vacuum filtration onto a Büchner funnel and washing with methanol yielded a white crystalline solid (PF = 33%, ACV = 2.62 mmol/g). The desired p-methyl allylether polystyrene (**3-19**) was pumped dry to give 1.558 g (74% yield). ^{1}H NMR integration indicated a 99% displacement of reactive sites (PC = 99%). ^{1}H NMR ($CDCl_3$)δ: 1.0-2.3 (m, 10H), 3.98 (m, 2H), 4.42 (m, 2 H), 5.27 (m, 2 H), 5.94 (m, 1H), 6.14-7.40 (m, 14H).

Dibutyltin Chloride Polymer (3-20)

A solution was made of **3-19** (8.08 g, 21.0 mmol) and dibutyltin dichloride (10.2 g, 33.6 mmol) in 20 mL benzene under argon in a sealed pyrex tube. Slowly, dibutyltin dihydride[20b] (7.9 g, 34 mmol) was added and the solution was irradiated with a Hanovia 450 nm mercury lamp for 8 h. The solution was then poured into 400 mL of vigorously stirring methanol. The liquid was decanted and 50 mL fresh MeOH was added. The suspension was cooled to –78°C to solidify the product, and the solid was rinsed well before collecting by vacuum filtration. The product (ACV = 1.53 mmol/g, PF = 33%) was pumped to dryness to yield the desired dibutyltin chloride polymer (**3-20**) as a white-gray solid (12.74 g, 93% yield). ^{1}H NMR integration indicated a 92% incorporation of tin at the active sites. ^{1}H NMR ($CDCl_3$)δ: 0.8-2.1 (m, 36 H), 3.3 (m, 2H), 4.4 (m, 2H), 6.1-7.2 (m, 14 H).

Adamantane (3-15)

A solution was made of 1-bromoadamantane (**3-13**) (50 mg, 0.23 mmol) in DMA (0.19 M, 1.3 mL). AIBN (4 mg, 0.1 equiv) was added, followed by decane (35 mg, 0.24 mmol, 1.1 equiv) as an internal standard. Lastly, $NaBH_4$ (14 mg, 0.35 mmol) and **3-20** (15 mg, 0.1 equiv) were added. The solution was heated to 80 °C and after 2 h, a GC sample was taken to evaluate the efficiency of the reaction. Comparison of product peak with that of the decane standard indicated 99% conversion.

The solution was diluted with ether, extracted twice with water, then once with brine and dried with Na_2SO_4. Next the solvent was evaporated and the product was purified by column chromatography. Adamantane **3-15** was isolated as a white solid (38 mg, 60% yield). **3-15** was identical in all respects to an original sample purchased from the Aldrich Chemical Co.

Iodinated protected D-xylose (3-25)

Sample provided by Dr. Eric Enholm: ^{1}H NMR($CDCl_3$)δ: 1.32 (s, 3 H), 1.52 (s, 3H), 2.23 (d, 1H, J=5.1 Hz), 3.29 (m, 2H), 4.43 (m, 2H), 4.57 (d, 1H, J=3.6Hz), 5.99 (d, 1H, J=3.6 Hz); ^{13}C NMR ($CDCl_3$) δ: -1.2, 26.2, 26.8, 74.8, 80.8, 85.0, 105.5, 112.1; HRMS(EI) calcd for $C_8H_{13}IO_4$ (M+) 299.9859, found 299.9834.

Protected 5-deoxy D-xylose (3-26)

A solution was made of the iodinated protected D-xylose (**3-25**) (100 mg, 0.333 mmol) in DMA (0.19 M, 1.75 mL). AIBN (6 mg, 0.1 equiv), $NaBH_4$ (19 mg, 0.5 mmol) and **3-20** (22 mg, 0.1 equiv) were added. The solution was heated to 85 ºC and after 1 h, TLC indicated reaction was complete. The crude reaction was applied directly to column chromatography. Pure **3-26** was isolated as an oil (49 mg, 85% yield). ^{1}H NMR($CDCl_3$)δ: 1.31 (s, 6 H), 1.50 (s, 3H), 2.33 (s, br, 1H), 3.99 (d, 1H, J=2.4 Hz), 4.31 (m, 1H, J=2.7, 6.6 Hz), 4.52 (d, 1H, J= 3.6 Hz), 5.89 (d, 1H, J=3.6 Hz); ^{13}C NMR ($CDCl_3$)δ: 12.71, 26.05, 26.49, 76.02, 76.18, 85.46, 104.30, 111.34; IR(Neat) cm^{-1}: 1013.3, 1073.6, 1165.8, 1215.7, 1374.9, 1627.3, 3445.1; HRMS(EI) calcd for $C_8H_{15}O_4$ (M+1) 175.0970, found 175.0952.

Dodecane (3-28)

A solution was made of dodecyl iodide (**3-28**) (100 mg, 0.373 mmol) in DMA (0.19 M, 2.0 mL). AIBN (6 mg, 0.1 equiv), $NaBH_4$ (21 mg, 0.56 mmol) and **3-20** (24 mg, 0.1 equiv) were added. The solution was heated to 85 °C and after 30 min, TLC indicated reaction was complete. The crude reaction was applied directly to column chromatography. Pure **3-28** was isolated as a colorless liquid (56 mg, 88% yield). **3-28** was identical in all respects to an original sample purchased from the Aldrich Chemical Co.

Phenyl propane (3-30)

A 0.19 M solution was made of 2-bromo-1-phenyl propane (**3-29**) (988 mg, 4.92 mmol) in 10 mL DMA and 16 mL of benzene. AIBN (80 mg, 0.1 equiv), $NaBH_4$ (280 mg, 7.39 mmol) and **3-20** (32 mg, 0.01 equiv) were added. After degassing with argon, the solution was heated to 85 °C. After 4 h, more AIBN (40 mg) was added and the solution continued to heat for a total of 6.5 h. After evaporating benzene, the crude reaction was applied directly to column chromatography and eluted with pentanes. Fractions containing the product were combined and concentrated on rotor-evaporator without heat. Pure **3-30** was isolated as a colorless liquid (550 mg, 93% yield). Spectral data for **3-30** is identical in all respects to that reported by Hendrickson.[77]

Anthracene (3-32)

A solution was made of 9-bromoanthracene (**3-31**) (100 mg, 0.389 mmol) in DMA (0.19 M, 2.0 mL). AIBN (6 mg, 0.1 equiv), $NaBH_4$ (22 mg, 0.58 mmol) and **3-20** (26 mg, 0.1 equiv) were added. The solution was heated to 85 ºC for 2.5 h, then more $NaBH_4$ (15 mg, 0.39 mmol) was added. After heating for 30 min longer, GC showed the reaction was complete. The crude reaction was added to 100 mL brine, and the solid residues were filtered off. The solid was extracted into hot hexane and washed with water. After evaporating the hexane layer, pure **3-32** was isolated (55 mg, 80% yield). **3-32** was identical in all respects to an original sample purchased from the Aldrich Chemical Co.

Fluorene (3-34)

A solution was made of 95% 2-bromofluorene (**3-33**) (105 mg, 0.408 mmol) in DMA (0.1 M, 4 mL). AIBN (13 mg, 0.2 equiv), $NaBH_4$ (39 mg, 1.0 mmol) and **3-20** (53 mg, 0.082 mmol) were added. The solution was heated to 70 ºC for 23 h, then the crude reaction was added to 100 mL brine, and the solid residues were filtered off. The solid was extracted into hot hexane and washed with water. After evaporating the hexane layer, pure **3-33** was isolated (50 mg, 74% yield). **3-33** was identical in all respects to an original sample purchased from the Aldrich Chemical Co.

1,2-Isopropylidene-3-O-phenyl-chlorothionoformate-5-O-diphenyl-t-butylsilyl-β-xylofuranose (3-35)

A sample was provided by Dr. Eric Enholm. ^{1}H NMR($CDCl_3$)δ: 1. 07(s, 9H), 1.35(s, 3H), 1.56(s, 3H), 3.97(d, 2H, J=6.9 Hz), 4.56(m, 1H), 4.79(d, 1H, J=3.9 Hz), 5.63-5.79(m, 1H), 5.97(d, 1H, J=3.9 Hz), 7.02(d, 2H, J=7.8 Hz), 7.20-7.73(m, 13H); ^{13}C NMR ($CDCl_3$) δ: 19.2, 26.3, 26.7, 60.3, 78.8, 82.8, 85.1, 104.9, 112.3, 121.7, 127.6, 127.7, 127.8, 129.5, 129.8, 132.9, 133.0, 134.7, 135.4, 153.2, 194.0; IR(KBr) cm^{-1}: 894, 1277, 1427, 1590, 3070, 3518; Anal. calcd for $C_{32}H_{36}O_6SiS$: C, 65.93; H, 6.43. Found: C, 66.01, H, 7.57.

1,2-Isopropylidene-5-O-diphenyl-t-butylsilyl-β-xylofuranose (3-36)

A solution was made of (**3-35**) (71 mg, 0.13 mmol) in DMA (0.19 M, 0.7 mL). AIBN (2.1 mg, 0.1 equiv), $NaBH_4$ (7 mg, 0.2 mmol) and **3-20** (8 mg, 0.1 equiv) were added. The solution was heated to 85 °C for 1.5 h, then the crude reaction was cooled to rt and diluted with 100 mL ether. The ether solution was extracted thrice with brine and then dried over Na_2SO_4. After evaporating the organic layer the crude product was columned. Pure **3-36** was isolated (26 mg, 47% yield). ^{1}H NMR($CDCl_3$)δ: 1. 05(s, 9H), 1.33(s, 3H), 1.47(s, 3H), 4.11(m, 4H), 4.37(s, 1H), 4.55(d, 1H, J=3.9 Hz), 6.00(d, 1H, J=3.6 Hz), 7.35-7.73(m, 10H); ^{13}C NMR ($CDCl_3$)δ: 19.1, 26.2, 26.7, 26.8, 62.8, 76.6, 78.4, 85.4, 105.0, 111.5, 127.9, 130.0, 131.9, 135.5, 135.7; IR (KBr)cm^{-1}: 708, 821, 1011, 1116, 1219, 1388, 1428, 2855, 3470; Anal. calcd for $C_{24}H_{32}O_5Si$: C, 67.26; H, 7.53. Found: C, 67.35, H, 7.56.

Ylide 4-13a

A solution of triphenylphosphine (43.0 g, 151 mmol) in benzene (325 mL, 0.51 M) was stirred at rt with a mechanical stirrer. Triethylamine (6.0 mL, 43 mmol) was added, followed by a solution of 2-bromoacetophenone (**4-12a**) (30.0 g, 151 mmol) in benzene (300 mL, 0.50 M). As the reaction stirred at rt for an additional 2 h, a white precipitate formed. Methanol (250 mL) was added to dissolve the precipitate, the solution stirred for 30 min longer, then solvent was removed by reduced pressure. The crude ylide salt was collected by Büchner filtration and washed with THF (300 mL).

The resulting crude ylide salt was placed in hot H_2O (500 mL) and NaOH (s) (30 g, 750 mmol) was added very slowly with stirring. The solution was cooled in an ice bath and the yellow precipitate was collected by Büchner filtration. The crude product was recrystallized by dissolving in hot benzene (350 mL), decolorizing with charcoal, and hot filtration. The filtrate was evaporated by reduced pressure and hexane was added to the resulting residue. After chilling on ice, the solid was collected by Büchner filtration and washed with hexane.

The pure white solid **4-13a** was collected (40.83 g, 71%) m.p. 181-183 °C. ^{1}H NMR ($CDCl_3$)δ:4.42(d, 1H, J=24 Hz), 7.32-7.38(m, 3H), 7.42-7.60(m, 9H), 7.67-7.78(m, 6H), 7.93-8.01(m, 2H); ^{13}C NMR($CDCl_3$)δ:126.47, 126.89, 127.71, 128.76, 128.93, 129.32, 132.02, 133.07, 133.19, 184.87.

5-Trimethylsilyl-4-pentynal (4-15a), 4-pentynal (4-15b), and 5-hexynal (4-15c)

The method developed by Swern[45a] was used, all oxidations being spot-to-spot. After workup, ^{1}H NMR and ^{13}C NMR taken of the crude aldehydes indicated they were fairly pure. Due to the unstable nature of the aldehyde products, the crude materials were not chromatographed, but used immediately in their respective Wittig reactions. **4-15b** was identical in all respects to that reported by Bierer and Kabalka.[45b] **4-15c**: ^{1}H NMR($CDCl_3$)δ:1.86(m, 2H), 1.98(s, 1H), 2.27(m, 2H), 2.60(m, 2H), 9.80(s, 1H); ^{13}C NMR($CDCl_3$)δ:17.69, 20.74, 42.44, 69.29, 83.08, 201.56.

1-Phenyl-7-trimethylsilyl-2-hepten-6-yn-1-one (4-9a), 1-phenyl-2-hepten-6-yn-1-one (4-9b), and 1-phenyl-2-octen-7-yn-1-one (4-9e)

The following general procedure is representative: The crude 5-trimethylsilyl-4-pentynal (**4-15a**) (12.82 mmol, 1equiv, assuming the oxidation proceeded at 100%) with ylide **4-13a** (9.743 g, 25.64 mmol, 2 equiv) was dissolved in dry $CHCl_3$ (21 mL, 0.6 M). The soln. was stirred 4-10 h at reflux. Removal of the solvent by reduced pressure and purification by chromatography provided 1-phenyl-7-trimethylsilyl-2-hepten-6-yn-1-one (**4-9a**) (2.165 g, 66% yield from 2 steps) as a faint yellow oil. Enones **4-9b** and **4-9e** were similarly produced as light yellow oils with yields of 66% and 69% (2 steps) respectively from their appropriate alcohols.

4-9a: ^{1}H NMR($CDCl_3$) δ: 0.01(s, 9H), 2.35(m, 4H), 6.86(m, 2H), 7.36(m, 3H), 7.80(m, 2H); ^{13}C NMR($CDCl_3$)δ: 0.03, 18.86, 31.65, 85.87, 105.38, 126.94, 128.46, 128.50, 132.63, 137.76, 146.79, 190.68; IR(Neat)cm^{-1}: 696.1, 759.9, 840.6, 969.4, 1249.5, 1286.1, 1448.0, 1622.6, 1673.9, 2175.2, 3059.8; HRMS(EI) calcd for $C_{16}H_{20}OSi$ 256.1282, found 256.1263.

4-9b: ^{1}H NMR($CDCl_3$) δ:2.05(t, 1H, J=2.7 Hz), 2.39(m, 2H), 2.51(m, 2H), 7.00(m, 2H), 7.48(m, 3H), 7.93(m, 2H); ^{13}C NMR($CDCl_3$)δ:17.22, 31.21, 69.41, 82.55, 126.58, 128.27, 128.75, 132.47, 137.44, 146.33, 190.12; IR(Neat) cm^{-1}: 694.5, 966.7, 1232.5, 1286.8, 1350.5, 1447.9, 1623.9, 1670.3, 3058.8, 3295.6; HRMS(EI) calcd for $C_{13}H_{12}O$ 184.0888, found 184.0895.

4-9e: ^{1}H NMR($CDCl_3$)δ:1.74(pent, 2H, J=6.6 Hz), 2.01(t, 1H, J=3.0 Hz), 2.24(dt, 2H, J=6.6 Hz), 2.44(q, 2H, J=6.6 Hz), 6.98(m, 2H), 7.50(m, 3H), 7.92(m, 2H); ^{13}C NMR($CDCl_3$)δ:17.75, 26.66, 31.35, 69.00, 83.34, 126.35, 128.34, 132.50, 137.67, 148.08, 190.32; IR(Neat)cm^{-1}: 694.7, 772.0, 975.1, 1227.0, 1283.9, 1447.9, 1620.8, 1670.3, 2116.3, 3297.1; HRMS(EI) calcd for $C_{14}H_{14}O$ 198.1045, found 198.1048.

2-Hepten-6-ynal (4-9c) and 3-octen-7-yn-2-one (4-9d)

The following general procedure is representative: Crude 4-pentynal (**4-15b**) (30.5 mmol, 2 equiv, assuming oxidation proceeded 100%) was prepared as described above and commercially available (triphenylphosphoranylidene)-acetaldehyde (**4-13b**) (5.0 g, 16 mmol, 1 equiv) were added to $CHCl_3$ (25 mL, 0.7 M). The solution was refluxed overnight, the solution concentrated by reduced pressure evaporation, and chromatographic purification was performed. The pure 2-hepten-6-ynal (**4-9c**) (1.363 g, 77% yield from 2 steps) was isolated as an oil. Similarly, by reacting 4-pentynal (**4-15b**) with commercial 1-triphenyl-phosphoranylidene-2-propanone (**4-13c**), 3-octen-7-yn-2-one (**4-9d**) was isolated as an oil in 84% yield (from 2 steps).

4-9c: ^{1}H NMR ($CDCl_3$)δ:2.07(t, 1H, J=2.7 Hz), 2.43(m, 2H), 2.57(m, 2H), 6.18(m, 1H), 6.91(dt, 1H, J=15.6, 6.6 Hz), 9.52(d, 1H, J=13.8 Hz); ^{13}C NMR ($CDCl_3$)δ:16.94, 31.06, 69.66, 82.06, 133.48, 155.28, 193.48; IR(NaCl)cm^{-1}: 967.1, 1125.7, 1689.8, 2355.1, 3283.5; HRMS(CI) calcd for C_7H_9O (M+1) 109.0653, found 109.0623.

4-9d: ^{1}H NMR($CDCl_3$)δ:2.07(t, 1H, J=2.1 Hz), 2.26(s, 3H), 2.41(m, 4H), 6.13(d, 1H, J=16.2 Hz), 6.83(dt, 1H, J=16.2, 6 Hz); ^{13}C NMR($CDCl_3$)δ:16.94, 26.40, 30.68, 69.29, 82.17, 131.69, 144.95, 197.72; IR(NaCl)cm^{-1}:974.1, 1255.6, 1362.2, 1432.0, 1628.3, 1675.3, 3292.4; HRMS(CI) calcd for $C_8H_{11}O$ (M+1) 123.0810, found 123.0847.

7-Dodecen-11-yn-6-one (4-9f)

A solution was prepared of commercially available dimethyl(2-oxoheptyl)-phosphonate (**4-16**) (1.0 g, 4.5 mmol) and anh. K_2CO_3 (s) (1.86 g, 13.5 mmol) in H_2O (2.25 mL). The solution was stirred at rt for 4 h. A solution of crude 4-pentynal (**4-15b**) (0.481 g, 5.86 mmol) in THF (2.0 mL, 2.9 M) was added and the solution was stirred for 48 h. The solution was condensed by reduced pressure evaporation. Some H_2O was added and the product was extracted into a solution of 1:1 ether/hexane. After Na_2SO_4 drying and removal of solvent, the crude enone was purified by column chromatography. The pure 7-dodecen-11-yn-6-one (**4-9f**) (0.555g, 69% yield) was isolated as a colorless oil. ^1H NMR($CDCl_3$) δ:0.89(t, 3H, J=6.6 Hz), 1.31(m, 4H), 1.61(pent, 2H, J=6.6 Hz), 2.03(s, 1H), 2.40(m, 4H), 2.54(m, 2H), 6.15(d, 1H, J=15.9 Hz), 6.82(dt, 1H, J=15.9, 6.6 Hz); ^{13}C NMR($CDCl_3$) δ:13.64, 17.21, 22.20, 23.60, 30.90, 31.17, 39.85, 69.26, 82.36, 130.94, 143.72, 200.11; IR(NaCl)cm^{-1}:636.1, 733.2, 915.4, 1632.0, 1674.0, 1697.7, 2119.7, 3309.0; HRMS(CI) calcd for $C_{12}H_{19}O$ (M+1) 179.1436, found 179.1421.

(2-methylidenecyclopentyl)phenylmethanone (4-11b) and (2-methyl-1-cyclopentyl)phenylmethanone (4-19b)

A solution of 1-phenyl-2-hepten-6-yn-1-one (**4-9b**) (500 mg, 2.72 mmol) in benzene (14 μL), with AIBN (89 mg, 0.54 mmol) and tributyltin hydride (20 M, 800 μL, 2.99 mmol) was prepared and degassed with argon for 5 min. The solution was refluxed for 30-45 min, monitoring by TLC for disappearance of starting material. The solution was cooled to ambient temperature, whereupon anhydrous $HgCl_2$ (812 mg, 2.99 mmol), HMDS (114 μL, 0.54 mmol) and CH_2Cl_2 (13.6 mL) were added. The reaction solution was stirred at rt. for 45 min, after which TLC indicated the tin enolate had been consumed. The solution was cooled to 0°C and NaI (1.74 g, 10.9 mmol), THF (5.4 mL) and 5M HCl (2.17 mL, 10.9 mmol) were added. The stirred solution was allowed to warm to rt over 4 h then diluted with CH_2Cl_2 and neutralized with Na_2CO_3 (s).

The solid was removed via filtration, the solution condensed and column chromatography provided (2-methylidenecyclopentyl) phenylmethanone (**4-11b**) (362 mg, 72%) and (2-methyl-1-cyclopentyl) phenylmethanone (**4-19b**) (76 mg, 15 %) as light yellow oils. Combined isolated yield = 87 %.

4-11b: ^{1}H NMR($CDCl_3$)δ:1.67-2.52(m, 6H), 4.37(t, 1H, J=7.4 Hz),4.72(m, 1H, J=2.1 Hz), 5.02(m, 1H, J=2.1),7.45-7.61(m,3H),8.00(m, 2H); ^{13}C NMR ($CDCl_3$)δ:25.16, 30.78, 34.12, 50.97, 108.50, 128.76, 128.91, 132.87, 137.30, 151.94, 201.00; HRMS(EI) calcd for $C_{13}H_{14}O$ 186.1045, found 186.1039.

4-19b: ^{1}H NMR($CDCl_3$)δ:1.68(s, 3H), 1.92(pent, 2H, J=6.6 Hz),2.53(m, 2H), 2.76(m, 2H),7.40-7.57(m,3H),7.75(m, 2H); ^{13}C NMR ($CDCl_3$)δ:16.71, 22.19, 35.77, 40.48, 128.36, 128.82, 132.25, 136.16, 139.15, 150.02, 197.18; HRMS(EI) calcd for $C_{13}H_{14}O$ 186.1045, found 186.1041.

byproducts 1-phenyl-6-hepten-1-one (4-17b) and byproduct 1-phenyl-6-heptyn-1-one (4-18b)

The procedure for **4-11b** was followed, using 0.25 equiv tributyltin hydride [or 0.15 equiv $(Bu_3Sn)_2O$] and 1 equiv $PhSiH_3$. After initial reflux for 45 min to form the enolate, the remaining reagents were added in the method described above. The only products isolated were **4-17b** and **4-18b**. Product **4-17b** can be avoided by excluding $PhSiH_3$ and initially heating for no more than 15 min during enolate formation. **4-18b** forms when enolate **4-10** is quenched too soon with HCl. This can be avoided by allowing longer reaction times for the carbo-mercuration step.

4-17b: ^1H NMR ($CDCl_3$) δ:1.49 (m, 2H), 1.76(p, 2H, J=7.5 Hz), 2.11(q, 2H, J=7.5 Hz), 2.98(t, 2H, J=7.5 Hz), 4.99(m, 2H), 5.82(m, 1H), 7.40-7.63(m, 3H), 7.96(m, 2H); ^{13}C NMR($CDCl_3$) δ:23.79, 28.57, 33.56, 38.39, 114.62, 128.02, 128.54, 132.88, 137.02, 138.52, 200.32; IR(Neat)cm^{-1}: 690.8, 752.8, 912.0, 1001.5, 1685.1, 3064.9; HRMS(EI) calcd for $C_{13}H_{16}O$ (M+1) 188.1201, found 188.1210.

4-18b: ^1H NMR($CDCl_3$) δ:1.64 (m, 2H), 1.81-1.96(m, 3H), 2.25(dt, 2H, J=3, 9 Hz), 3.00(t, 2H, J=9 Hz), 7.39-7.60(m, 3H), 7.96(m, 2H); ^{13}C NMR($CDCl_3$)δ: 18.30, 23.31, 28.01, 37.91, 68.58, 84.09, 128.02, 128.57, 132.97, 136.93, 199.91; IR(Neat)cm^{-1}: 690.9, 752.5, 1224.6, 1448.4, 1597.6, 1685.1, 3060.4, 3297.6 ; HRMS(EI) calcd for $C_{13}H_{14}O$ (M+) 186.1045, found 186.1041.

(2-Methylidenecyclohexyl)phenylmethanone (4-11e)

A solution of 1-phenyl-2-octen-7-yn-1-one (**4-9e**) (200 mg, 1.01 mmol) in benzene (50 μL), with AIBN (53 mg, 0.32 mmol) and tributyltin hydride (20 M, 430 μL, 1.60 mmol) was prepared and degassed with argon for 5 min. The solution was refluxed for 20 min, monitoring by TLC for disappearance of starting material. The solution was cooled to ambient temperature, anhydrous $HgCl_2$ (700 mg, 2.58 mmol), HMDS (50 μL, 0.24 mmol) and CH_2Cl_2 (4.3 mL) were added. The reaction solution was stirred at 30° C overnight. The solution was cooled to 0°C and NaI (735 mg, 4.59 mmol), THF (2.25 mL) and 5M HCl (0.9 mL, 4.5 mmol) were added. The stirred solution was allowed to warm to rt. over 3 h then diluted with CH_2Cl_2 and neutralized with Na_2CO_3 (s). The solid was removed via filtration, the solution condensed and column chromatography provided (2-methylidenecyclohexyl)phenylmethanone (**4-11e**) (84 mg, 42 %). ^1H NMR ($CDCl_3$)δ:1.45-2.02(m, 6H), 2.22(m, 1H), 2.40(m, 1H), 3.99(m, 1H), 4.44(s, 1H), 4.80(s, 1H), 7.46(m, 3H), 7.95(m, 2H); ^{13}C NMR($CDCl_3$)δ:24.54, 28.30, 30.08, 35.83, 51.48, 109.81, 128.42, 132.68, 137.07, 148.69, 201.70.

Methyl-1-bromocyclopentanecarboxylate (5-22a) and Methyl-1-bromocyclohexanecarboxylate (5-22b)[60]

The procedure employed by Lange was followed. Compounds **5-22a** and **5-22b** were isolated in 83% and 93% yields, respectively. Spectral data for **5-22b** was identical in all respects to that reported by Lange.[60]

Methyl-1-cyclopentene-1-carboxylate (5-23a) and Methyl-1-cyclohexene-1-carboxylate (5-23b)[60]

The procedure employed by Lange was followed. Compounds **5-23a** and **5-23b** were isolated in 75% and 98% yields, respectively. Spectral data for **5-23b** was identical in all respects to that reported by Lange.[60]

Methyl-3-oxo-1-cyclopentene-1-carboxylate (5-24a)[52] and Methyl-3-oxo-1-cyclohexene-1-carboxylate (5-24b)[60]

The procedure employed by Lange was followed. Compounds **5-24a** and **5-24b** were isolated in 33% and 51% yields, respectively. Spectral data for **5-24a** and **5-24b** were identical in all respects to that reported by Lange.[52, 60]

3-Phenylcyclohex-2-en-1-one (5-27)[63]

The procedure employed by Woods was followed. Compound **5-27** was isolated in 53% yield. ^{1}H NMR($CDCl_3$)δ:2.14(m, 2H), 2.47(m, 2H), 2.76(m, 2H), 6.42(s, 1H), 7.39(m, 3H), 7.54(m, 2H); ^{13}C NMR($CDCl_3$)δ: 22.78, 28.06, 37.23, 125.36, 126.03, 128.71, 129.93, 138.74, 159.72, 199.74; IR (Nujol) cm^{-1}: 700.1, 769.1, 1456.0, 1653.3; exact mass (EI) for $C_{12}H_{12}O$ (M+) calcd 172.0888, found 172.0931.

General Irradiation Procedure for [2+2] Photoadditions

The appropriate amounts of cyclic enone (**5-24a,b** or **5-27**) and cycloalkene (**5-28a** or **5-28b**) were dissolved in the indicated solvent and placed in a dry 25mL Pyrex test tube with stirbar. The tube was sealed with a rubber septum and the solution was degassed with nitrogen for 2 min with stirring. The vessel was irradiated until the conclusion of the reaction, as followed by GC and TLC analysis (typically 5-8 h). The solvent was removed by rotor-evaporator and the crude products were purified by chromatographic separation on a silica absorption column.

Methyl-8-oxotricyclo[5.3.0.0^{2,6}]decane-1-carboxylate (5-14a)[52]

The procedure employed by Lange was followed. Compound **5-14a** was isolated as a mixture of anti/syn diastereoisomers (6:1) in 92% yield. Spectral data for **5-14a** is identical in all respects to that reported by Lange.[52]

Methyl-5-oxotricyclo[5.4.0.0^{2,6}]undecane-2-carboxylate (5-14b)[53a]

The procedure employed by Lange was followed. Compound **5-14b** was isolated as a mixture of anti/syn diastereoisomers in 93% yield. Spectral data for **5-14b** is identical in all respects to that reported by Lange.[53a]

Methyl-8-oxotricyclo[5.4.0.0^{2,6}]undecane-1-carboxylate (5-14c)[52]

A 0.2 M solution containing 1 g of **5-24b** and 2.21 g (5 equiv) of cyclopentene (**5-28a**) was prepared in 30 mL anhydrous ether. After normal preparation of the solution and irradiation for 3.5 h. The cis-anti-cis and cis-syn cis diastereomer products had formed in a 9:1 ratio, respectively. Upon purification, 1.23 g of a yellow oil was collected (86% yield). Spectral data agreed with that reported previously.[52]

Methyl-9-oxotricyclo[6.4.0.0^{2,7}]dodecane-1-carboxylate (5-14d)[53a]

A solution of 340 mg **5-24b** and 542 mg of cyclohexene (**5-28b**) in 15 mL dry t-BuOH and 1 mL MeOH was prepared in the usual manner. Irradiation for 8 h and subsequent purification produced 392 mg of a yellow oil (95% yield), with the cis-anti-cis product favored over the cis-syn-cis diastereomer (7:4). Spectral data agreed with that reported previously.[53a]

1-Phenyltricyclo[6.4.0.0^{2,7}]-9-dodecanone (5-14e)[64]

300 mg (1.74 mmol) of **5-27** and 716 mg (5 equiv) of cyclohexene (**5-28b**) were dissolved in 15 mL dry t-BuOH and 5 mL MeOH. The solution was irradiated for 6.5 h. 430 mg of two diastereomeric products were collected (97% yield) in a ratio of 4:1, as determined by GC. It has been demonstrated from

examples in the current literature that the cis-anti-cis diastereomer would be preferred over the cis-syn-cis product. [64] ^1H NMR($CDCl_3$)δ: 1.16-1.98(m, 14H), 2.28-2.56(m, 2H), 2.84(d, 1H, J=9.9 Hz), 6.92-7.34(m, 5H); ^{13}C NMR($CDCl_3$)δ: 21.2, 26.0, 26.3, 27.4, 29.8, 31.0, 39.2, 43.9, 52.0, 54.3, 56.4, 125.5, 125.8, 128.2, 150.2, 211.8; IR (Neat) cm^{-1}: 702.7, 760.0, 1444.6, 1493.9, 1602.2, 1692.3, 3023.7, 3057.5; exact mass (EI) for $C_{18}H_{22}O$ (M+) calcd 254.1671, found 254.1666.

6-Oxo-2-phenylbicyclo[6.4.0]dodecane (5-15)

A solution was prepared in a 25 mL pear-shaped flask by dissolving **5-14e** (258 mg, 1.02 mmol) in 9 mL of distilled benzene. 0.2 equiv of AIBN and 1.5 equiv of tributyltin hydride (410 μL, 1.53 mmol) were added. The solution was refluxed at 85°C overnight. After purification by silica absorption chromatography, 214 mg of an oily product (89% yield) was collected. ^1H NMR($CDCl_3$)δ:0.5-2.5(m, 17H); 7.2(m, 5H); IR (KBr disk) cm^{-1}: 702.6, 758.3, 1031.9, 1447.2, 1696.2, 3456.7; exact mass (FAB) for $C_{18}H_{25}O$ (M+H) calcd 257.1905, found 257.1905.

Methyl-8-hydroxytricyclo[3.3.1.0.0]undecane-1-carboxylate (5-16a)

In a 5 mL pear-shaped flask 276 mg of **5-14c** was dissolved in 780 μL distilled benzene and 1 mL (3 equiv) tributyltin hydride with 123 mg AIBN were added. The solution was refluxed with stirring for 12.5 h. The solution was allowed to cool and benzene was evaporated off. The solution was diluted with 5 mL of ether and 590 μL (3.2 equiv) of DBU added, stirring for 2 h longer. A solution of I_2 in ether was added until the color persisted. After concentrating the crude product and purifying on a silica column, 190 mg of a yellow oil (68% yield) was isolated. **5-16a:** ^{1}H NMR($CDCl_3$)δ:1.0-1.94(m, 12H), 2.23(m, 1H), 2.43(m, 1H), 2.66(m, 1H), 2.76(m, 1H), 3.68(s, 3H), 3.84(m, 1H); ^{13}C NMR($CDCl_3$)δ: 21.1, 26.7, 28.2, 30.8, 32.2, 33.7, 34.8, 41.9, 47.8, 48.8, 51.4, 67.8, 176.1; IR (KBr disk) cm^{-1}: 733.0, 1048.9, 1449.5, 1726.5, 3445.8; exact mass (FAB) for $C_{13}H_{21}O_3$ (M+H) calcd 225.1491, found 225.1475, $C_{13}H_{19}O_2$ (M+H-H_2O) calcd 207.1385, found 207.1395.

Methyl-9-hydroxytricyclo[4.3.1.0.0]dodecane-1-carboxylate (5-16b)

In a 10 mL pear-shaped flask 150 mg of **5-14d** was dissolved in 4.5 mL distilled benzene and 410 μl (2.25 equiv) tributyltin hydride with 15 mg AIBN were added. The solution was refluxed with stirring for 11.5 h, at which point the GC showed no starting material left at this point. For workup, to the cooled solution was added 10 mL of MeOH and then the solution was concentrated by the rotor-evaporator. The crude product was next dissolved in 15 mL ether, 2.3 equiv of DBU was added with a drop of water, and a solution of I_2 in ether was added until the color remained. The mixture was stirred for 20 min, then the solution was concentrated and the crude material was purified on a silica column. The pure product **5-16b** was isolated as a yellow-white solid (73 mg), along with 63 mg of unreacted **5-14d** (46% yield from recovered starting material). **5-16b**: ^{1}H NMR ($CDCl_3$) δ:1.0-2.3(m, 17H), 2.15(s, 1H), 2.68(s, 1H), 3.71(s, 3H); ^{13}C NMR ($CDCl_3$)δ: 25.2, 26.0, 27.0, 31.4, 31.7, 40.4, 42.5, 48.3, 51.2, 51.9, 52.0, 65.0, 91.7, 176.9; IR(Nujol)cm^{-1}: 1022.8, 1209.9, 1377.5, 1453.5, 1706.3, 3464.7; exact mass (FAB) for $C_{14}H_{23}O_3$ (M+H) calcd 239.1647, found 239.1635.

Methyl-8-hydroxytricyclo[5.3.0.0^{2,6}]decane-1-carboxylate (5-29)

In a 5 mL round bottom, a 0.5 M solution of **5-14a** (52 mg, 0.25 mmol) was made in 0.5 mL ethanol. At room temperature, 18 mg of $NaBH_4$ (0.48 mmol, 2 equiv) was added and the reaction stirred for 30 min. The solution was diluted with ether and extracted with H_20, followed by brine. After drying the organic layer with $MgSO_4$ and evaporating the solvent, the pure product **5-29** was obtained (46 mg, 87% yield). ^{1}H NMR($CDCl_3$)δ:1.40-2.08(m, 11H), 2.46(m, 2H), 2.55(m, 1H), 3.66(s, 3H), 4.27(m, 1H); ^{13}C NMR($CDCl_3$)δ: 18.2, 25.4, 30.1, 31.6, 32.8, 33.8, 46.7, 47.1, 51.1, 58.1, 74.1, 175.6; IR (KBr disk) cm^{-1}: 1707.7, 3418.0; exact mass (CI) for $C_{12}H_{19}O_3$ (M+1) calcd 211.1334, found 211.1389.

1-Phenyl-3-tridecanol (6-10) and 2-Benzyl-3-hydroxy-5-phenylpentanal (6-11)

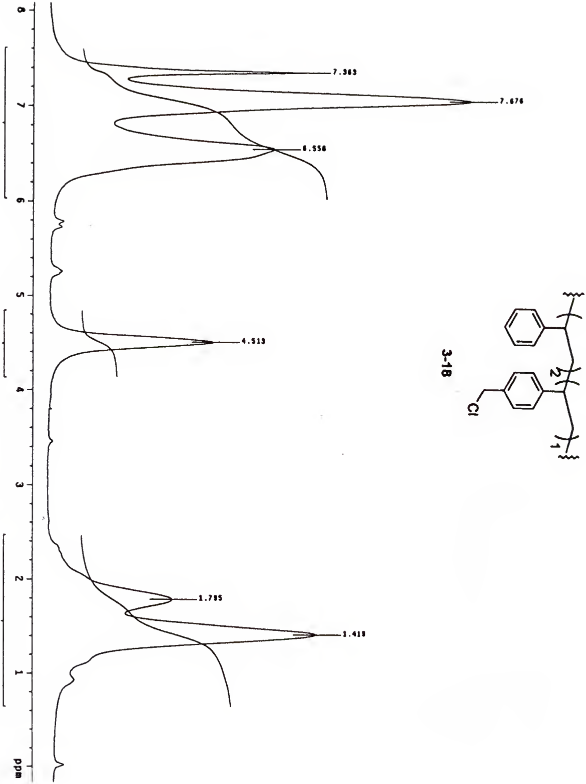
A 1 M solution of hydrocinnimaldehyde (**6-9**) (98 μL, 0.75 mmol) in CH_2Cl_2 (646 μL) was made under argon at –78°C. Tributyltin hydride (502 μL, 1.87

mmol), iododecane (1.6 mL, 7.5 mmol), triethylborane (1 M, 1.87 mL, 1.87 mmol), and BF_3OEt_2 (189 μL, 1.49 mmol) were added sequentially, keeping the temperature below 0°C. The reaction was stirred for 1.5 h, allowing it to warm to rt. After diluting with ether and quenching with H_2O, the organic layer was extracted with brine and then dried. Next, the solvent was removed by vacuum and the crude product was purified by column chromatography. The pure alkylated product **6-10** was isolated as a white solid (65 mg, 32%), as well as the aldol byproduct **6-11** (35 mg, 16%).

6-10: ^1H NMR($CDCl_3$) δ:1.17-1.60(m, 21H), 1.63-1.87(m, 2H), 1.96(s, 1H), 2.54-2.94(m, 2H), 3.60(s, br, 1H), 7.19(m, 5H); ^{13}C NMR($CDCl_3$) δ:14.03, 22.62, 25.58, 29.28, 29.57, 29.65, 31.85, 32.00, 37.51, 39.00, 71.17, 125.62, 128.25, 128.29, 142.18; IR (Nujol) cm^{-1}: 698.1, 748.3, 1094.4, 1345.9, 1453.7, 3025.3, 3358.1; HRMS(EI) calcd for $C_{19}H_{32}O$ (M+) 276.2453, found 276.2430.

APPENDIX
SPECTRAL DATA

The ^{1}H NMR spectra of selected compounds reported in Chapter 3 are illustrated in this appendix. The spectra along with the proposed structure are shown.



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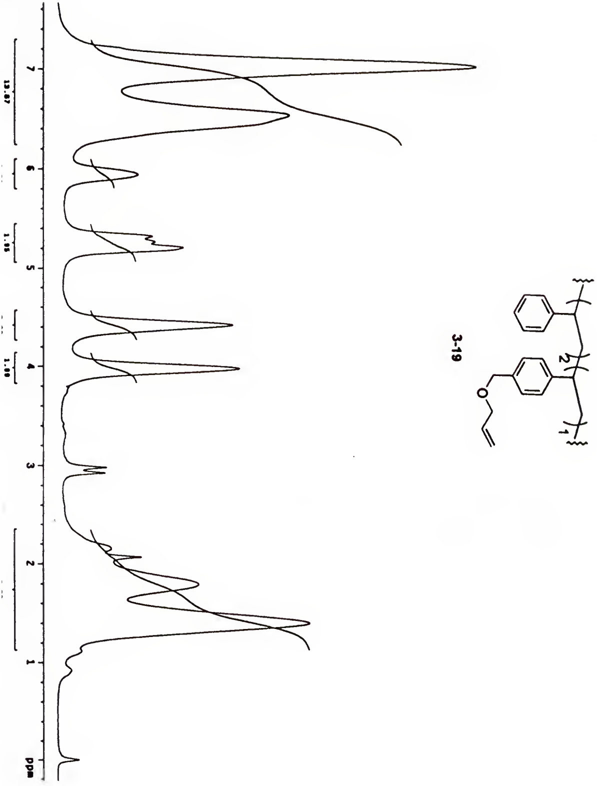

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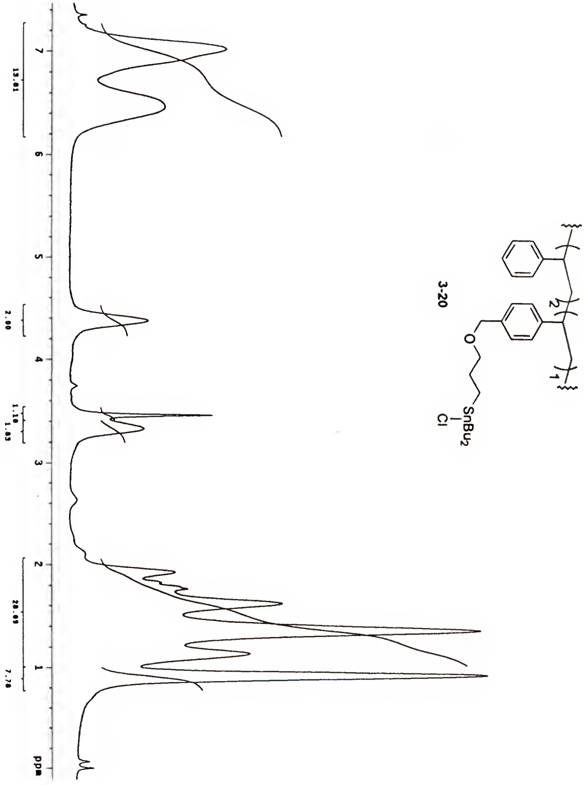

3-20

LIST OF REFERENCES

1. a) "Free Radical Chain Reactions in Organic Synthesis", W. B. Motherwell and D. Crich, Academic Press, London, **1992**; b) "Tin in Organic Synthesis", M. Pereyre, J-P. Quintard, and A. Rahm, Butterworth & Co. Ltd., London, **1987**.

2. C. Chatgilialoglu, *Acc. Chem. Res.* **1992**, *25*, 188-194.

3. a) A. Martinez-Grau and D. P. Curran, *Tetrahedron* **1997**, *53*(16), 5679-5689; b) M. Lesage, C. Chatgilialoglu, D. Griller, *Tetrahedron Lett.* **1989**, *30* (21), 2733-2734; c) A. Alberti and C. Chatgilialoglu, *Tetrahedron* **1990**, *46*(11), 3963-3972.

4. a) G. A. Kraus and S. Liras, *Tetrahedron Lett.* **1990**, *31* (37), 5265-5268; b) J. Curtice, H. Gilman, and G. S. Hammond, *J. Am. Chem. Soc.* **1957**, *79*, 4754-4759; c) C. Chatgilialoglu, K. U. Ingold, and J. C. Scaiano, *J. Am. Chem. Soc.* **1982**, *104*, 5119-5123.

5. a) K. U. Ingold, J. Lusztyk, and J. C. Scaiano, *J. Am. Chem. Soc.* **1984**, *106*, 343; b) V. H. Rawal, V. Krishnamurthy, and A. Fabre, *Tetrahedron Lett.* **1993**, *34*(18), 2899-2902.

6. J. Y. Godet and M. Pereyre, *Bull. Soc. Chim. Fr.* **1976**, 1105.

7. J. P. Pete and M. L. Viriot-Villaume, *Bull. Soc. Chim. Fr.* **1971**, 3699.

8. K. J. Kulicke and B. Giese, *Synlett.* **1990**, 91-92.

9. a) G. J. M. Van Derkerk, J. G. Noltes, and J. G. A. Luijten, *J. Appl. Chem.* **1957**, 7, 356; b) E. J. Enholm, P. E. Whitley, Y. Xie, *J. Org. Chem.* **1996**, *61*, 5384-5390; c) E. J. Enholm and K. S. Kinter, *J. Am. Chem. Soc.* **1991**, *113*, 7784-7785; d) E. J. Enholm, Y. Xie, and K. A. Abboud, *J. Org. Chem.* **1995**, *60*, 1112-1113.

10. J. E. Baldwin, *J. Chem. Soc., Chem. Commun.* **1976**, 734.

11. a) K. M. Chen, G. E. Hardtmann, K. Prasad, O. Repic, and M. J. Shapiro, *Tetrahedron Lett.* **1987**, *28*, 155-158; b) F. G. Kathawala, B. Prager, K. Prasad, O. Repic, M. J. Shapiro, R. S. Stabler, and L. Widler, *Helv. Chim. Acta.* **1986**, *69*, 803-805.

12. a) C. Fuganti, P. Grasselli, S. Servi, F. Spreafico, and C. Zirotti, *J. Org. Chem.* **1984**, *49*(21), 4087-4089; b) T. Fujisawa, E. Kojima, T. Itoh, and T. Sato, *Tetrahedron Lett.* **1985**, *26*(49), 6089-6092.

13. a) D. P. Curran, *Synthesis* **1988**, 417-439, 489-513; b) S. Kim, C. Y. Hong, and S. Yang, *Angew. Chem. Int. Ed. Engl.* **1983**, *22*(7), 562; c) E. J. Corey and J. W. Suggs, *J. Org. Chem.* **1975**, *40*(17), 2554-2555.

14. a) N. L. Drake and G. B. Cooke, *Org. Synth. II* **1943**, 406; b) L. A. Walker, *Org. Synth. III* **1955**, 757; c) S. Ramachandran and M. S. Newman, *Org. Synth.* **1961**, *41*, 38.

15. J. A. Cusumano, *Chem. Tech.* **1992**, *22*, 482.

16. a) D. Schummer, G. Höfle, *Synlett.* **1990**, 705; b) "Handbook of Toxic and Hazardous Chemicals", M. Sittig, Noyes Publications, New Jersey, **1981**; c) "Registry of Toxic Effects of Chemical Substances 1985-1986", vol. 5, D. V. Sweet, **1986**.

17. a) C. Chatgilialoglu, *Chem. Rev.* **1995**, *95,*1229-1251; b) I. Fleming, Organic Silicon Chemistry, IN *Comp. Org. Chem.,* Sir D. Barton and W. D. Ollis, Pergamon, New York, **1979**, *vol. 3,* Chp. 13, 541-686; c) D. A. Armitage, Organosilanes, IN *Comp. Orgmet. Chem. II*, E. W. Abel, F. G. A. Stone, G. Wilkinson, Pergamon, New York, **1982**, *vol. 2,* Chp. 1, 1-44.

18. T. G. Selin and R. West, *J. Amer. Chem. Soc.* **1962**, *84,* 1860.

19. H. Gilman, W. H. Atwell, P. K. Sen, C. L. Smith, *J. Organomet. Chem.* **1965**, *4,* 163.

20. a) D. P. Curran, C. T. Chang, *J. Org. Chem.* **1989**, *54*, 3140; b) U. Gerigk, M. Gerlach, W. P. Neumann, R. Vieler, V. Weintritt, *Synthesis* **1990**, 448-452.

21. E. L. Eliel and Y. Senda, *Tetrahedron* **1970**, *26*, 2411.

22. H. O. House, *Modern Synthetic Reactions, 2nd ed.,* **1972**, 155.

23. J. A. Schreier, Ph.D. dissertation, U. of Fl., **1995**, 60.

24. C. Chatgilialoglu, A. Guerrini, G. Seconi, *Synlett* **1990**, 219.

25. a) A. D. Allen, J. C. Charlton, C. Eaborn, G. Modena, *J. Chem. Soc.* **1957**, 3668; b) A. D. Allen and G. Modena, *J. Chem. Soc.* **1957**, 3671.

26. M. E. Havill, I. Joffe, H. W. Post, *J. Org. Chem.* **1948**, *13,* 280.

27. J. Jia, Ph.D. dissertation, U. of Fl., **1996**, 88.

28. a) R. B. Merrifield, *J. Am. Chem. Soc.* **1963**, *85*, 2149-2154; b) C. C. Leznoff, *Acc. Chem. Res.* **1978**, *11*, 327-333; c) E. Camps, J. Cartells, and J. Pi, *Anales de Quimica* **1974**, *70*, 848-849; d) J. M. J. Frechet and C. Schuerch, *J. Am. Chem. Soc.* **1971**, *93*, 492-496.

29. a) P. T. Ho, D. Chang, J. W. X. Zhong, and G. F. Musso, *Peptide Research*, **1993**, *6*, 10-12; b) C. G. Boojamra, K. M. Burow, and J. A. Ellman, *J. Org. Chem.* **1995**, *60*, 5742-5743.

30. P. H. H . Hermkens, H. C. J. Ottenheijm, and D. Rees, *Tetrahedron* **1996**, *52*(13), 4527-4554.

31. "Catalog Handbook of Fine Chemicals", Aldrich Chemical Co. **1989-1990**.

32. M. Narita, *Bull. Chem. Soc. Jap.* **1978**, *51*, 1477.

33. a) X. Du and R. W. Armstrong, *J. Org. Chem.* **1997**, *62*, 5678-5679; b) F. Gasparrini, D. Misiti, C. Villani, A. Borchardt, M. T. Burger, and W. C. Still, *J. Org. Chem.* **1995**, *60*, 4314-4315; c) A. Routledge, C. Abell, and S. Balasubramanian, *Synlett* **1997**, 61.

34. M. P. Sibi and S. V. Chandramouli, *Tetrahedron Lett.* **1997**, *38*(52), 8929-8932.

35. M. Gerlach, F. Jordens, H. Kuhn, W. P. Neumann, and M. Peterseim, *J. Org. Chem.* **1991**, *56*(21), 5971-5972.

36. G. Dumartin, M. Pourcel, B. Delmond, O. Donard, and M. Pereyre, *Tetrahedron Lett.* **1998**, *39*, 4663-4666.

37. S. Chen and K. D. Janda, *Tetrahedron Lett.* **1998**, *39*, 3943-3946.

38. J. M. Conia and P. Le Perchec, *Synthesis* **1975**, *I*, 1-19.

39. a) W. Oppolzer, E. J. Jacobseri, *Tetrahedron Lett.* **1986**, 1141, 5467; b) W. Oppolzer, Metallo-ene Reactions, IN *Comp. Org. Syn.*, B. M. Trost and I. Fleming, Pergamon Press, **1991**, vol. *5*, chp. 1.2, 29-61.

40. a) J. Drouin, M-A Boaventura, J-M. Conia, *J. Am. Chem. Soc.* **1985**, *107*, 1726-1729; b) M-A Boaventura, J. Drouin, F. Theobald, N. Rodier, *Bull. Chim. Soc. Fr.* **1987**, *6*, 1006-1026.

41. a) C. J. Forsyth and J. Clardy, *J. Am. Chem. Soc.* **1990**, *112*, 3497-3505; b) H. Huang and C. J. Forsyth, *Tetrahedron Lett.* **1993**, *34*(49), 7889-7890.

42. M. D. Mizhiritskii and Y. A. Yuzhelevskii, *Russ. Chem. Rev.* **1987**, *56*, 355-365.

43. F. Ramirez and S. Dershowitz, *J. Org. Chem.* **1957**, *22*, 41.

44. K. Fukui, R. Sudo, M. Masaki, M. Ohta, *J. Org. Chem.* **1968**, *33*, 3504.

45. a) A. J. Mancuso, S-L Huang, D. Swern, *J. Org. Chem.* **1978**, *43*(12), 2480-2482; b) D. E. Bierer and G. W. Kabalka, *Org. Prep. Proced. Int.* **1988**, *20*(1), 63.

46. B. E. Maryanoff and A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863-927.

47. P. Seguineau and J. Villieras, *Tetrahedron Lett.* **1988**, *29*(4), 477.

48. a) J. Y. Godet, M. Pereyre, *J. Organometal. Chem.* **1972**, *40*, C23; b) M. Castaing, M. Pereyre, M. Ratier, P. M. Blum, and A. G. Davies, *J. Chem. Soc. Perkin II*, **1979**, 589.

49. J. Y. Godet and M. Pereyre, *J. Organometal. Chem.* **1974**, *77*, C1.

50. M. T. Crimmins, S. Huang, and L. E. Guise-Zawacki, *Tetrahedron Lett.* **1996**, *37*(36), 6519-6522.

51. J. D. Winkler and V. Sridar, *J. Am. Chem. Soc.* **1986**, *108*(7), 1708-1709.

52. G. L. Lange C. P. Decicco, J. Willson and L. A. Strickland, *J. Org. Chem.* **1989**, *54*, 1805-1810.

53. a) G. L. Lange and C. Gottardo, *J. Org. Chem.* **1995**, *60*(26), 2183-2187; b) G. L. Lange and C. Gottardo, Tetrahedron Lett. **1994**, *35*(46), 8513-8516.

54. J. Kupka, T. Anke, B. M. Giannetti and W. Steglich, *Arch. Microbiol.* **1981**, *130*, 223.

55. Heatley et al., *Brit. J. Exp. Pathol.* **1947**, *28*, 35.

56. M. Kaneda, R. Takahashi, Y. Iitaka and S. Shibata, *Tetrahedron Lett.* **1972**, 4607.

57. E. Ayanoglu, T. Gebreyesus, C. M. Beechan and C. Djerassi, *Tetrahedron* **1979**, *35*, 1035.

58. a) L. V. Hijfte, R. D. Little, J. L. Petersen and K. D. Moeller, *J. Org. Chem.* **1987**, *52*(21), 4647-4661; b) B. M. Trost, C. D. Shuey, F. DiNinno, Jr., and S. S. McElvain, *J. Am. Chem. Soc.* **1979**, *101*(5), 1284-1285; c) E. J. Corey, M. C. Desai and T. A. Engler, *J. Am. Chem. Soc.* **1985**, *107*(14), 4339-4341; d) W. A. Kinney, M. J. Coghlan and L. A. Paquette, *J. Am. Chem. Soc.* **1984**, *106*(22), 6868-6870.

59. a) M. T. Crimmins and T. L. Reinhold, Enone Olefin [2+2] Photochemical Cycloadditions, IN Organic Reactions, *vol. 44*, John Wiley & Sons, Inc., New York, **1993**, 297-588; b) M. T. Crimmins, *Chem. Rev.* **1988**, *88*, 1453-1473.

60. G. L. Lange and J. A. Otulakowski, *J. Org. Chem.* **1982**, *47*(26), 5096-5099.

61. a) C. Hell, *Ber.* **1881**, *14*, 891; b) J. Volhard, *Ann.* **1887**, *242*, 141; c) N. Zelinsky, *Ber.* **1887**, *20*, 2026.

62. K. B. Sharpless, A. Y. Teranishi and J. E. Bäckvall, *J. Am. Chem. Soc.* **1977**, *99*, 3120-3128.

63. G. F. Woods and I. W. Tucker, *J. Am. Chem. Soc.* **1948**, *70*, 2174-2176.

64. R. M. Bowman, C. Calvo, J. J. McCullough, W. Rasmussen, and F. F. Snyder, *J. Org. Chem.* **1972**, *37*(13), 2084-2091.

65. a) K. Nozaki, K. Oshima, and K. Utimoto, *J. Amer. Chem. Soc.* **1987**, *109*, 2547-2549; b) K. Miura, K. Oshima, and K. Utimoto, *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2356-2364.

66. a) K. Miura, Y. Ichinose, K. Nozaki, K. Fugami, K. Oshima, and K. Utimoto, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 143; b) Y. Ichinose, S. Matsunaga, K. Fugami, K. Oshima, and K. Utimoto, *Tetrahedron Lett.* **1989**, *30*, 3155.

67. a) K. Goodall and A. F. Parsons, *Tetrahedron Lett.* **1997**, *38*(3), 491-494; b) M. Ihara, A. Katsumata, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. I* **1997**, 991-992.

68. a) K. Nozaki, K. Oshima, and K. Utimoto, *Tetrahedron* **1989**, *45*(4), 923-933; b) K. Nozaki, K. Oshima, and K. Utimoto, *Tetrahedron Lett.* **1988**, *29*(47), 6125-6126; c) D. H. R. Barton, D. O. Jang, and J. Cs. Jaszberenyi, *Tetrahedron Lett.* **1990**, *31*(33), 4681-4684; d) L. Ripa and A. Hallberg, *J. Org. Chem.* **1998**, *63*, 84-91.

69. P. Devin, L. Fensterbank, and M. Malacria, *Tetrahedron Lett.* **1998**, *39*, 833.

70. M. P. Sibi and J. Ji, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*(3), 274-276.

71. H. Miyabe, R. Shibata, C. Ushiro, and T. Naito, *Tetrahedron Lett.* **1998**, *39*, 631-634.

72. a) H. C. Brown and M. M. Midland, *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 692-700; b) H. C. Brown, M. M. Midland, and G. W. Kabalka, *Tetrahedron* **1986**, *42*, 5523.

73. J. B. Hendrickson, M. Singer, and Md. S. Hussoin, *J. Org. Chem.* **1993**, *58*, 6913-6914.

BIOGRAPHICAL SKETCH

James P. Schulte II was born in Grand Rapids, Michigan, the second largest city in the state, on March 1, 1971. He was the youngest of six children, which included Kurt, Kris, Eric, Karla and Paul. His father Jim (I) was an electrical engineer and his mother Barbara was a mathematics teacher. As family legend has it, his parents ran out of names for the children and so James (II) was born.

Growing up in the Schulte household was quite an experience. There was never a time when some animal (usually a large dog) didn't occupy residency there. A large contingency of canines has succeeded through that family's history, ranging from beagle to German shepherd to Doberman. Although cats were considered second-class pets, they were occasionally tolerated, and ultimately were loved too.

Being raised in such a large family provided many opportunities for mischief and ample experiences, often at the expense of the parents. Needless to say, the Schulte clan composed quite a team and endeavored into several sports including baseball, soccer, football, and bowling. This interactive background established a strong sense of camaraderie for Jim, which follows him today.

At a young age, Jim was privileged to attend excellent schools with accelerated programs. In the sixth grade, his hard work enabled him to enroll at John Ball Park Zoo School, in Grand Rapids, Michigan. Here, he learned first-hand about zoology and botany. Later in middle school, Jim attended City High School, where advanced learning was the norm. Because the school was so small, some classes had to be taken at the nearby Central High School. Here, it was during his junior year when Mr. Lubbers first introduced Jim to chemistry.

Until that time, Jim had strong ambitions to enter into law enforcement. He had served internships with both the Grand Rapids Police Department and the Kent County Sheriff's Department. The tide had turned though; the strong influence of Bella Lugosi and Vincent Price's 'mad scientist' films, along with the exciting hands-on chemistry lab proved to be too enticing. From that point on, Jim endeavored to become a chemist and devoted his efforts to that end.

In the fall of 1989, Mr. Schulte enrolled into the chemistry program at Michigan State University. As soon as he could, he began independent research, working for Dr. Paul Hunter, Dr. Chi Chang, and finally Dr. Eugene LeGoff. Jim immediately discovered his knack for organic chemistry and tried to learn as much as he could absorb.

Jim chose the University of Florida for graduate school in 1994, recognizing a strong organic faculty there. He worked under Dr. Eric Enholm, expanding his knowledge and expertise into synthetic organic chemistry. After graduation, Mr. Schulte plans to work in industry, exploiting his talents for their use in practical applications.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Eric Enholm, Chairman
Associate Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Merle A. Battiste

Merle Battiste
Professor of Chemistry

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James Deyrup
Professor of Chemistry

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James Boncella
Associate Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

David Clark

David Clark
Professor of Materials Science
and Engineering

This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

December, 1998

Dean, Graduate School